

**IMPLEMENTING THE 21ST CENTURY CURES ACT:
AN UPDATE FROM FDA AND NIH**

HEARING
BEFORE THE
SUBCOMMITTEE ON HEALTH
OF THE
COMMITTEE ON ENERGY AND
COMMERCE
HOUSE OF REPRESENTATIVES
ONE HUNDRED FIFTEENTH CONGRESS
FIRST SESSION

NOVEMBER 30, 2017

Serial No. 115-82



Printed for the use of the Committee on Energy and Commerce
energycommerce.house.gov

U.S. GOVERNMENT PUBLISHING OFFICE

28-733

WASHINGTON : 2019

COMMITTEE ON ENERGY AND COMMERCE

GREG WALDEN, Oregon
Chairman

JOE BARTON, Texas <i>Vice Chairman</i>	FRANK PALLONE, JR., New Jersey <i>Ranking Member</i>
FRED UPTON, Michigan	BOBBY L. RUSH, Illinois
JOHN SHIMKUS, Illinois	ANNA G. ESHOO, California
MICHAEL C. BURGESS, Texas	ELIOT L. ENGEL, New York
MARSHA BLACKBURN, Tennessee	GENE GREEN, Texas
STEVE SCALISE, Louisiana	DIANA DEGETTE, Colorado
ROBERT E. LATTA, Ohio	MICHAEL F. DOYLE, Pennsylvania
CATHY McMORRIS RODGERS, Washington	JANICE D. SCHAKOWSKY, Illinois
GREGG HARPER, Mississippi	G.K. BUTTERFIELD, North Carolina
LEONARD LANCE, New Jersey	DORIS O. MATSUI, California
BRETT GUTHRIE, Kentucky	KATHY CASTOR, Florida
PETE OLSON, Texas	JOHN P. SARBANES, Maryland
DAVID B. McKINLEY, West Virginia	JERRY McNERNEY, California
ADAM KINZINGER, Illinois	PETER WELCH, Vermont
H. MORGAN GRIFFITH, Virginia	BEN RAY LUJAN, New Mexico
GUS M. BILIRAKIS, Florida	PAUL TONKO, New York
BILL JOHNSON, Ohio	YVETTE D. CLARKE, New York
BILLY LONG, Missouri	DAVID LOEBSACK, Iowa
LARRY BUCSHON, Indiana	KURT SCHRADER, Oregon
BILL FLORES, Texas	JOSEPH P. KENNEDY, III, Massachusetts
SUSAN W. BROOKS, Indiana	TONY CARDENAS, California
MARKWAYNE MULLIN, Oklahoma	RAUL RUIZ, California
RICHARD HUDSON, North Carolina	SCOTT H. PETERS, California
CHRIS COLLINS, New York	DEBBIE DINGELL, Michigan
KEVIN CRAMER, North Dakota	
TIM WALBERG, Michigan	
MIMI WALTERS, California	
RYAN A. COSTELLO, Pennsylvania	
EARL L. "BUDDY" CARTER, Georgia	
JEFF DUNCAN, South Carolina	

SUBCOMMITTEE ON HEALTH

MICHAEL C. BURGESS, TEXAS
Chairman

BRETT GUTHRIE, Kentucky <i>Vice Chairman</i>	GENE GREEN, Texas <i>Ranking Member</i>
JOE BARTON, Texas	ELIOT L. ENGEL, New York
FRED UPTON, Michigan	JANICE D. SCHAKOWSKY, Illinois
JOHN SHIMKUS, Illinois	G.K. BUTTERFIELD, North Carolina
MARSHA BLACKBURN, Tennessee	DORIS O. MATSUI, California
CATHY McMORRIS RODGERS, Washington	KATHY CASTOR, Florida
LEONARD LANCE, New Jersey	JOHN P. SARBANES, Maryland
H. MORGAN GRIFFITH, Virginia	BEN RAY LUJAN, New Mexico
GUS M. BILIRAKIS, Florida	KURT SCHRADER, Oregon
BILLY LONG, Missouri	JOSEPH P. KENNEDY, III, Massachusetts
LARRY BUCSHON, Indiana	TONY CARDENAS, California
SUSAN W. BROOKS, Indiana	ANNA G. ESHOO, California
MARKWAYNE MULLIN, Oklahoma	DIANA DEGETTE, Colorado
RICHARD HUDSON, North Carolina	FRANK PALLONE, JR., New Jersey (<i>ex officio</i>)
CHRIS COLLINS, New York	
EARL L. "BUDDY" CARTER, Georgia	
GREG WALDEN, Oregon (<i>ex officio</i>)	

CONTENTS

	Page
Hon. Michael C. Burgess, a Representative in Congress from the State of Texas, opening statement	1
Prepared statement	3
Hon. Gene Green, a Representative in Congress from the State of Texas, opening statement	4
Hon. Greg Walden, a Representative in Congress from the State of Oregon, opening statement	6
Prepared statement	7
Hon. Fred Upton, a Representative in Congress from the State of Michigan, prepared statement	8
Hon. Frank Pallone, Jr., a Representative in Congress from the State of New Jersey, opening statement	9
WITNESSES	
Scott Gottlieb, M.D., Commissioner, Food and Drug Administration	11
Prepared statement	14
Answers to submitted questions	90
Francis Collins, M.D., Director, National Institutes of Health	28
Prepared statement	31
Answers to submitted questions	104
SUBMITTED MATERIAL	
Statement of the Healthcare Leadership Council, submitted by Mr. Burgess ...	87

IMPLEMENTING THE 21ST CENTURY CURES ACT: AN UPDATE FROM FDA AND NIH

THURSDAY, NOVEMBER 30, 2017

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:03 a.m., in room 2123, Rayburn House Office Building, Hon. Michael Burgess, M.D. (chairman of the subcommittee) presiding.

Present: Representatives Burgess, Guthrie, Upton, Shimkus, Blackburn, Lance, Griffith, Bilirakis, Long, Bucshon, Brooks, Mullin, Hudson, Collins, Carter, Walden (ex officio), Green, Engel, Schakowsky, Matsui, Castor, Sarbanes, Luján, Schrader, Cárdenas, Eshoo, DeGette, and Pallone (ex officio).

Staff Present: Ray Baum, Staff Director; Karen Christian, General Counsel; Kelly Collins, Staff Assistant; Zachary Dareshori, Legislative Clerk, Health; Paul Edattel, Chief Counsel, Health; Adam Fromm, Director of Outreach and Coalitions; Caleb Graff, Professional Staff Member, Health; Jay Gulshen, Legislative Associate, Health; Ed Kim, Policy Coordinator, Health; Bijan Koochmaraie, Counsel, Digital Commerce and Consumer Protection; Katie McKeogh, Press Assistant; Alex Miller, Video Production Aide and Press Assistant; Mark Ratner, Policy Coordinator; Kristen Shatynski, Professional Staff Member, Health; Jennifer Sherman, Press Secretary; Danielle Steele, Counsel, Health; Hamlin Wade, Special Advisor, External Affairs; Greg Zerzan, Counsel, Digital Commerce and Consumer Protection; Jeff Carroll, Minority Staff Director; Waverly Gordon, Minority Health Counsel; Tiffany Guarascio, Minority Deputy Staff Director and Chief Health Advisor; Jessica Martinez, Minority Outreach and Member Services Coordinator; Samantha Satchell, Minority Policy Analyst; Kimberlee Trzeciak, Minority Senior Health Policy Advisor; and C.J. Young, Minority Press Secretary.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BURGESS. The subcommittee will now come to order.

The chair will recognize himself for 5 minutes for the purpose of an opening statement.

The 21st Century Cures Act was a monumental achievement. Cures was the product of a bipartisan, multiyear effort by the Energy and Commerce Committee that brought our laws into a modern era of medicine. It has been nearly 1 year since Cures was

signed into law. I remember remarking at that press conference a year ago to imagine a world in which government was not an obstacle but an ally in helping us deliver drugs and devices to patients and cures to patients. Today's hearing marks the Health subcommittee's first look into the implementation of what many in the healthcare community called a transformational bill that would positively impact not only the researchers and the scientists who are developing the latest breakthrough therapies, but physicians seeking treatment for their patients, giving hope to them, their loved ones, and other advocates.

This morning we will hear from two leaders responsible for implementing the drug development and biomedical research provisions included in Cures. I want to welcome Dr. Francis Collins, the Director of National Institutes of Health, and Dr. Scott Gottlieb, Commissioner of the Food and Drug Administration, both back to this subcommittee. All of us know the demands your schedules put on both of you, and we appreciate you coming before us today.

At the time of the Energy and Commerce Committee's launch of the 21st Century Cures initiative, the statement was made repeatedly that there were 500 cures and treatments to address 10,000 known diseases. More progress was needed to alleviate the agony of an incurable disease.

While the United States had maintained its global leadership in biomedical innovation, there existed a potential bridge in the growing divide between the revolutionary advances in science and technology and a less-than-adequate system for discovering, developing, and delivering new therapies.

Members of the committee, both this committee and the Senate HELP Committee, held numerous public hearings, forums, roundtables in Washington, D.C., and around the country bringing together leading scientists and medical experts, patient and disease group advocates, and researchers across multiple sectors. The primary objective of these events was to uncover opportunities to strengthen and streamline the process by which cures are discovered and made available to patients. Cures accelerated the cycle of discovery, development, and delivery of new treatments and ensured that the United States remained at the helm of biomedical innovation.

At the National Institutes of Health, the 21st Century Cures Act authorized resources to support biomedical research and reduce administrative burdens and provided almost \$5 billion in new funding to support the agency's four innovation projects. The Precision Medicine Initiative was authorized for \$1.4 billion for the National Institutes of Health to build to a national biomedical dataset in order to accelerate health research and medical breakthroughs. The bill also authorized \$1.5 billion for the Brain Research through Advancing Innovative Neurotechnologies Initiative to better understand the brain's physiology and to coordinate efforts across multiple Federal and private groups to expedite research for diseases like Alzheimer's.

Cures also authorized \$1.8 billion for cancer prevention, cancer diagnosis, cancer treatment and care through the Beau Biden Cancer Moonshot. Finally, the Regenerative Medicine Innovation Project was authorized at \$30 million to support clinical research

in the field of regenerative medicine in coordination with the Food and Drug Administration.

The 21st Century Cures Act helped the Food and Drug Administration modernize the regulation of medical products throughout its lifecycle. It established the “FDA Innovation Account” and authorized \$500 million in funding to implement Title III of the law, which included a broad range of deliverables from the Food and Drug Administration. These include creating a mechanism for the collection and incorporation of patient perspectives in regulatory decisionmaking, updating the way medical products are reviewed and approved, and advancing new drug therapies through a review pathway for biomarkers and other drug development tools to help shorten the development time while maintaining the same rigorous standard for safety and effectiveness. It also required the Food and Drug Administration to establish standards and definitions necessary to develop regenerative medicines.

Before I close, I recognize the 21st Century Cures Act also touched upon other critical healthcare priorities, such as mental health and health information technology. Both of these areas should have their own separate hearings because of their importance to the medical community, and those are on the list for the very near future.

I again want to welcome our witnesses and thank you for being here. I look forward to your testimony.

My time has expired, and I will yield to the gentleman from Texas, Mr. Green, the ranking member of the subcommittee, 5 minutes for an opening statement, please.

[The prepared statement of Mr. Burgess follows:]

PREPARED STATEMENT OF HON. MICHAEL C. BURGESS

The Subcommittee will come to order.

The Chair will recognize himself for an opening statement.

The 21st Century Cures Act (Cures) was a monumental achievement. Cures was the product of a bipartisan, multi-year effort by the Energy and Commerce Committee that brought our laws into a modern era of medicine. It has been nearly one year since Cures was signed into law. Today’s hearing marks the Health Subcommittee’s first look into the implementation of what many in the healthcare community called a transformational bill that would positively impact not only the researchers and scientists who are developing the latest breakthrough therapies, but physicians seeking treatments for their patients—giving hope to them, their loved ones, and other advocates.

This morning we will hear from two leaders responsible for implementing the drug development and biomedical research provisions included in Cures. I want to welcome Dr. Francis Collins, Director of the National Institutes of Health, and Dr. Scott Gottlieb, Commissioner of the Food and Drug Administration, back to this subcommittee. All of us know the demands of your schedules and appreciate both of you coming before us today.

At the time of the Energy and Commerce Committee’s launch of the 21st Century Cures Initiative, there were only 500 cures or treatments to address the 10,000 known diseases. Certainly, more progress was needed to alleviate the agony of an incurable disease.

While the U.S. had maintained its global leadership in biomedical innovation, there existed a potential to bridge the growing divide between the revolutionary advances in science and technology over the last decade and a less-than-adequate system for discovering, developing, and delivering new therapies. Members of the committee and the Senate HELP Committee held numerous public hearings, forums, and roundtables in Washington, D.C. and across the nation, bringing together leading scientists and medical experts, patient and disease group advocates, and researchers across multiple sectors. The primary objective of these events was to un-

cover opportunities to strengthen and streamline the process by which cures are discovered and made available to patients. Cures accelerated the cycle of discovery, development, and delivery of new treatments and ensured our nation remained at the helm of biomedical innovation.

At the NIH, the 21st Century Cures Act authorized resources to support biomedical research and reduce administrative burdens and provided almost \$5 billion dollars in new funding to support the agency's four innovation projects. The Precision Medicine Initiative was authorized over \$1.4 billion for NIH to build a national biomedical data set in order to accelerate health research and medical breakthroughs. Cures also authorized \$1.5 billion dollars for the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative to better understand the brain's physiology and coordinate efforts across multiple federal and private groups to expedite research for diseases like Alzheimer's. Cures also authorized \$1.8 billion dollars for cancer prevention, diagnosis, treatment and care through the Beau Biden Cancer Moonshot. Finally, the Regenerative Medicine Innovation Project was authorized \$30 million dollars to support clinical research in the field of regenerative medicine in coordination with the Food and Drug Administration (FDA).

The 21st Century Cures Act helped the FDA modernize the regulation of medical products throughout its lifecycle. It established an "FDA Innovation Account" and authorized \$500 million dollars in funding to implement Title III of the law, which included a broad range of deliverables from the FDA. These include creating a mechanism for the collection and incorporation of patient perspective in regulatory decision-making; updating the way medical products are reviewed and approved; advancing new drug therapies through a review pathway for biomarkers and other drug development tools to help shorten drug development time while maintaining the same rigorous standard for safety and effectiveness; and requiring the FDA to establish standards and definitions necessary to develop regenerative medicines.

Before I close, I recognize that the 21st Century Cures Act also touched upon other critical healthcare priorities, such as mental health and health IT. Both of these areas should have their own, separate hearings because of their importance to the medical community and I look forward to holding them in the near future.

I again want to welcome our witnesses and thank you for being here. I look forward to your testimony.

I would like to yield the balance of my time to Ms. Blackburn of Tennessee, for a statement.

OPENING STATEMENT OF HON. GENE GREEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. GREEN. Thank you, Mr. Chairman.

And thank you, Dr. Gottlieb and Dr. Collins, for being here this morning.

And I want to thank former Chairman Upton and Congresswoman DeGette for being the original cosponsors of the 21st Century Cures.

Next month will mark the 1-year anniversary of the 21st Century Cures Act being signed into law by President Obama in his last public signing ceremony. It was a great achievement, particularly at a time of hyperpartisanship and gridlock.

The work started long before 2016. In 2014, we set out on a mission to do something positive to boost medical research and innovation and accelerate the discovery, development, and delivery of new cures and treatments.

After countless hours devoted to roundtables, white papers, hearings, and drafts, Cures enjoyed bipartisan support and endorsements from over 700 organizations representing the full spectrum of stakeholders. It dedicated \$6.3 billion in new investments to support priorities like the Beau Biden Cancer Moonshot, the BRAIN Initiative, and the Precision Medicine Initiative within the National Institutes of Health to combat prescription drug abuse.

It also provides money to the FDA to advance the agency's mission and implement the policies in the underlying bill. This influx of investment is being put towards solving today's complex science problems, getting new treatments from the lab table to the bedside, and improving public health. Specifically, the NIH was provided \$4.8 billion in new funding to advance cutting-edge research initiatives.

The FDA was provided \$500 million over 10 years to improve the agency's medical product review process and expedite patient access to drugs and devices without compromising the safety and effectiveness standards.

In addition to this much needed funding, there were so many provisions in this package worthy of support, from facilitating development of new antibiotics, the fight against superbugs, to advancing the use of modern clinical trial designs, to fostering the next generation of medical researchers.

While some of the provisions are technical in nature, the real world impact they could have is not abstract. Patients and families deserve to have their elected officials respond to their needs, and this bill was an earnest attempt to do just that.

Like all negotiations and compromises, we didn't get everything we want, there is always more than can be done. But today is an opportunity to hear from the heads of FDA and NIH on implementation of things like patient-focused drug development, medical device innovation, improving science expertise and hiring capacity.

It is only been a year since passage. These things take time. But I know folks out in the respective agencies have been hard at work to get new initiatives off the ground and build on past efforts to advance medical research and development of new science.

While not the focus of today's hearing, Cures also included \$1 billion to combat the prescription drug abuse and overdose epidemic. The funding was significant but pales in comparison to what is needed to combat this crisis. There are more Americans dying from this epidemic than were at the height of the AIDS epidemic.

I hope this committee and Congress can fulfill its responsibilities to the American people and provide real and desperately needed funding to fight this epidemic that has raged in communities head-on. The 21st Century Cures demonstrates what we can accomplish when we work across the aisle, and I hope we can do so again.

I look forward to hearing from our witnesses about the ongoing implementation of 21st Century Cures.

And, Mr. Chairman, I want to yield the remainder of my time to Congresswoman DeGette.

Ms. DEGETTE. Thank you very much, Mr. Green, for yielding, and thank you for all of your work that you did on Cures. I am going to be sorry not to have you as my seat partner and my partner in issues like this in the next Congress. You have done a wonderful job.

And, Mr. Chairman, I want to thank you, too, for all the work you did on Cures.

Fred Upton of course is my partner and he was our chairman at the time. And we really wanted to do something bold and big when we started conceiving of 21st Century Cures, and I think we

achieved that. And so I am looking forward to hearing from our two witnesses today.

Dr. Gottlieb, your agency was a key partner, and I know you have carried on that effort. And of course Dr. Collins was there from the beginning with us, helping us craft this bill.

At one point I remember Dr. Collins said to me, very early on, he said, "You know, we just need to let our young researchers go to conferences." And I said, "If that is all we do, we will have failed."

And we did that and we did so much more. And so we are eager to hear how this bill has had impact in just 1 year, but we are even more eager to hear where we can take it next.

So thanks for all you do. Thanks to all of this committee for working together on this bill. And I yield back.

Mr. BURGESS. The chair thanks the gentlelady. The gentlelady yields back.

The chair recognizes the chairman of the full committee, the gentleman from Oregon, Mr. Walden, 5 minutes for an opening statement, please.

OPENING STATEMENT OF HON. GREG WALDEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OREGON

Mr. WALDEN. Thank you, Mr. Chairman. Thanks for having this oversight hearing, if you will, of an incredibly important lifesaving law that was passed in the last Congress in a bipartisan way. I think it was some of the finest work this committee has ever done.

And I know, Dr. Collins and Dr. Gottlieb, you haven't had anything else on your plate in the last year. But I say that facetiously, because you have had a lot, both of you have, and yet you seem to be doing a marvelous job implementing this vast bill and helping move forward to save lives and to improve the lives of families, friends, people we will never know.

And the consequences of this legislation are not confined to this hearing room, they are not confined to the District of Columbia, or even the United States. The research and the progress that will be made in these sectors will affect everyone in the world. This is world changing. My colleagues on both sides of the aisle have done marvelous work getting this done.

Now, my view has always been that once you pass a law, that is just the starting place. I know how difficult it was for Diana DeGette and Fred and Mike and Gene and everybody else to do this. But that was the starting point.

Today we look and say: What is it going forward? How is this working? Are these tools effective? Are there changes that need to be made? We know you are making great progress and we appreciate the terrific work you are doing.

I also want to recognize a very special guest here with us today, we have many in the room, but I want to draw special attention to somebody who has been part of this journey from the beginning, and that is young Mr. Max.

Max, we are delighted to have you here. You are an extraordinary young man. And we are so very glad that you are here to share in this special birthday appearance of the 21st Century Cures legislation. And it is because of people like you that inspire

us to do the best that this committee has to offer, the best work, the best legislation, because we know human lives are at stake.

With that, I am going to put——

[Applause.]

Mr. WALDEN. With that, I am going to submit my eloquently written opening statement into the record and defer the balance of my time to the former chairman of the committee, the chairman on Energy now, Fred Upton. And I know there are other members on our side who would like to share in what time remains.

So with that, I yield to the champion of 21st Century Cures and the improvement of people's lives around the world, my friend from Michigan, Mr. Upton.

[The prepared statement of Mr. Walden follows:]

PREPARED STATMENT OF HON. GREG WALDEN

Today the Subcommittee will review the implementation of critical components of the 21st Century Cures Act, a transformational law intended to modernize the nation's biomedical innovation infrastructure. Cures was signed into law in December of 2016, following a multi-year effort led by this committee to uncover opportunities to strengthen and streamline the process by which innovative medical products are discovered and made available to patients. I'd like to take this opportunity to commend our former Chairman, Fred Upton, as well as Representative Diana DeGette, for their unwavering dedication to getting this initiative across the finish line. I'd also like to recognize a very special guest who has been a part of this journey since the very beginning—Max, you are an extraordinary young man and we are so glad you could be here.

In our increasingly connected world where scientific innovation is outpacing government regulation, we have the potential to revolutionize medicine, and do more to reduce human suffering in the process. Over the course of two Congresses, members of this committee consulted with leading scientists and medical experts, patient and disease group advocates, and researchers and innovators across multiple sectors to find ways to accelerate a path to cures in America. We identified things the government could do to encourage innovation; and we also identified areas where government regulations and red tape were getting in the way of the revolutionary discoveries happening in labs across America. These initiatives culminated in the passage of the 21st Century Cures Act. By increasing research collaboration, improving personalized medicine, investing in the next generation of young investigators, removing regulatory uncertainty, providing new drug development incentives, and modernizing clinical trials, Cures sought to maintain and enhance America's global status as the leader in biomedical innovation, and above all, save lives.

I am proud of this committee's work to identify opportunities to improve our health care system, and to advance legislative solutions in a thoughtful, responsible, and bipartisan manner. The 21st Century Cures Act ushered in the changes necessary to bring our laws into a modern era of medicine. Today we will hear from the officials at the helm of implementing the research and development provisions authorized in the new law—NIH Director Francis Collins, and FDA Commissioner Scott Gottlieb. I look forward to hearing more about how these solutions are being implemented to keep our Nation at the forefront of innovation, and most importantly to deliver hope to millions of patients living with untreatable diseases.

Mr. UPTON. Well, thank you.

When we began the process of crafting 21st Century Cures 4 years ago, we began with one goal in mind, and that was helping patients and their families. And Diana DeGette, my great partner on the other side of the aisle, and I were inspired to act after hearing from folks in the research community, as well as patients and their families about the need for modernization and more resources at both the NIH and the FDA, to move quickly, bring lifesaving treatments to market.

And all of us had inspirations in our district. For me, it was two sisters, the Kennedy sisters, Brooke and Brielle, who have a rare genetic disease called spinal muscular atrophy, or SMA. Cures provided the NIH and the FDA with billions, tens of billions of dollars in much needed resources so that our Nation's best and brightest could work on finding cures for diseases that impact virtually every single family, whether it be cancer, diabetes, Lupus, or, yes, rare diseases like SMA.

And this hearing is a great thing for lots of reasons. Most notably, it is a reminder of how Republicans and Democrats came together to get a monumental piece of legislation signed into law despite our divided times. Diana worked with me on this as we worked for years and listened and worked to craft the language that would ultimately become law.

The hearing is also a reminder that we have a lot of work still to do. The Kennedy girls, our buddy Max in the front row, along with millions of patients and families across the country are counting on us.

And for that reason, I am immensely glad to welcome both Dr. Collins and Dr. Gottlieb on how the law is being implemented and what we in Congress can do to help that process a long and improve it.

I yield now to the gentlelady from Tennessee, Mrs. Blackburn.

[The prepared statement of Mr. Upton follows:]

PREPARED STATEMENT OF HON. FRED UPTON

When we began the process of crafting 21st Century Cures four years ago, we began with one goal in mind: Helping patients and their families. Diana DeGette, my partner on the other side of the aisle, and I were inspired to act after hearing from folks in the research community as well as patients and their families about the need for modernization and more resources at the NIH and FDA to more quickly bring lifesaving treatments to market.

Two of these inspirations were the Kennedy sisters—Brooke and Brielle—from Mattawan, Michigan. Brooke and Brielle have a rare genetic disease called Spinal Muscular Atrophy—or SMA.

Cures provides the NIH and the FDA with billions of dollars in much-needed resources so that our nation's best and brightest can work on finding cures for diseases that impact every single family.

Whether it be cancer, diabetes, lupus, or yes, rare diseases, like SMA.

This hearing is a great thing for many reasons. Most notably, it's a reminder of how Republicans and Democrats came together to get a monumental piece of legislation signed into law despite our divided times. Diana worked with me on this endeavor hand-in-glove for years—yes years—as we listened and worked to craft the language that would ultimately become law.

The hearing is also a reminder that we have much work left to do. The Kennedy girls, along with millions of patients and families across the country are counting on us. For that reason, I am immensely glad to welcome and thank Dr. Collins and Dr. Gottlieb for testifying before us today. I look forward to hearing from you both on how the law is being implemented and what we in Congress can do to help that process along.

Mrs. BLACKBURN. Thank you so much.

And we do welcome our witnesses, and we take this as an opportunity to thank you each for the help and the guidance that you have provided in what were then your roles and what are now your roles as we implement 21st Century Cures.

It is so appropriate that we do this hearing because, as you have heard, there was so much more that went into this than just saying

let's have people go to conferences or let's try. This was a way to change and reform the review and approval process so that it more adequately meets the innovation that is taking place in healthcare delivery systems.

So we welcome you.

We welcome Max and his bipartisan friends who have joined him this morning. What a great reminder, Max, that they have a reserved seat right there on the front row in sharing the success of this day.

Mr. Chairman, I thank you for the hearing, and I yield back.

Mr. WALDEN. And I yield back the balance of my time.

Mr. BURGESS. The chair thanks the gentleman. The gentleman yields back.

The chair recognizes the gentleman from New Jersey, Mr. Pallone, the ranking member of the full committee, 5 minutes, please.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Mr. Chairman.

I want to welcome Dr. Collins and Dr. Gottlieb here today to discuss the implementation of the 21st Century Cures Act. While the law addressed several different issues facing our healthcare system, such as the opioid epidemic and mental health, today we will be focusing on the ongoing work at NIH and FDA to implement the provisions of the law aimed at improving the discovery and development of new treatments and cures.

The Cures Act provided new funding to advance cutting-edge research at NIH. I am particularly proud that the law included funding for the Beau Biden Cancer Moonshot Initiative. This initiative aims to accelerate cancer research in America and improve our ability to prevent and detect cancers early on, and the hope is that one day we might find cures for the many different cancers, such as pancreatic cancer, that afflict patients today. I am interested in hearing how NIH is working to achieve this goal.

I am also pleased that the Cures Act invested new funds in the BRAIN Initiative and the Precision Medicine Initiative, which includes the All of Us Research Program. The BRAIN Initiative funds important research on brain disorders, such as Alzheimer's, epilepsy, and traumatic brain injury. And the All of Us Research Program funds a historic effort to gather data from at least a million people that will help lead to the development of personalized therapies rather than one-size-fits-all treatments.

At FDA, the Cures Act aims to bolster the medical product review process in order to get treatment to patients faster while also maintaining FDA's gold standard for safety and effectiveness. For example, the law granted FDA added authority to develop and utilize new tools to facilitate drug development, provide greater flexibility in the clinical trial process, and support the development of continuous manufacturing.

It also invested in increased patient engagement by encouraging the use of patient experience data in the review process. And the law also provided FDA with \$500 million in new funding to ensure

the agency has the necessary resources to recruit the best and brightest scientists and effectively implement the law.

And so I look forward to hearing more about the progress the agency has made to date on all of these issues.

And lastly, the Cures Act marked an important step towards the development of new treatments and cures. And I am pleased that the committee was able to work together on a bipartisan basis last Congress to pass this monumental law. And I of course particularly want to thank the chief sponsors, Fred Upton and Diana DeGette.

It is critical that we hold hearings to ensure the law is working as it should and achieving its goals. And I look forward to hearing from our witnesses today and to further discussions on implementation of other provisions of the law.

So I would like to yield the remainder of my time to Representative Luján.

Mr. LUJÁN. I thank the chairman and ranking member for organizing this hearing today and I thank the witnesses for their attendance.

Last Congress we worked together to pass the Comprehensive Addiction and Recovery Act and the 21st Century Cures Act. It is fair to say it was a compromise, not everyone got everything they wanted.

During the debate I pushed and have continued to advocate for more funding and resources to address the deadliest drug crisis in American history. We came together and we advanced legislation to provide \$1 billion over 2 years to strengthen the response to this crisis.

Still, 21st Century Cures Act's 2-year funding window creates planning problems for State and local governments. The uncertainty in funding to hire staff or plan beyond 2 years makes it difficult for people on the ground to do the work we are trying to empower them to do.

We must do more. That is why I introduced legislation to extend Cures funding to combat the opioid epidemic for an additional 5 years. Honestly, a 5-year extension of this funding is the minimum we should be doing.

I am grateful to the members of this committee who have cosponsored this bill, and I ask other members to add their voices to this effort. Let's work together to find common ground and move this.

Because this drug crisis is tearing apart the fabric of communities across the country, we must work together to ensure that this important funding does not expire. Too many people are suffering without access to meaningful support systems.

We must also step up our prevention efforts. One long-term avenue for prevention is the development of safe and effective, non-addictive opioids. We also need to move forward research and treatments that stop the craving of opioids and alcohol.

Dr. Gottlieb, I communicated with your office on this matter, and I understand the FDA is working with the NIH on a series of meetings to facilitate development of nonaddictive pain treatments. As you are aware, I sent you a letter on this issue. You responded by answering a few of the questions, but not all of the questions. I will be sending the letter again with expectations of more thorough an-

swers and responses to all of the questions, and I will also be submitting them into the record.

Mr. Chairman, thank you for again holding this hearing. And I yield back to Mr. Pallone.

Mr. BURGESS. The chair thanks the gentleman. The gentleman yields back.

This actually concludes member opening statements, and the chair would remind members, pursuant to committee rules, all members' opening statements will be made part of the record.

And again I want to thank and welcome our witnesses for being here today and taking their time to testify before the subcommittee. Each witness will have the opportunity to give an opening statement, and we will follow that with questions from the members.

This morning we are going to hear from Dr. Scott Gottlieb, the Commissioner of the Food and Drug Administration, and Dr. Francis Collins, the Director of the National Institutes of Health.

Dr. Gottlieb, we appreciate you being here today. Dr. Gottlieb, you are recognized for 5 minutes, please.

**STATEMENTS OF THE HONORABLE SCOTT GOTTLIEB, M.D.,
COMMISSIONER, FOOD AND DRUG ADMINISTRATION; AND
THE HONORABLE FRANCIS COLLINS, M.D., DIRECTOR, NA-
TIONAL INSTITUTES OF HEALTH**

STATEMENT OF SCOTT GOTTLIEB

Dr. GOTTLIEB. Thank you, Chairman Burgess, Ranking Member Green, members of the subcommittee. Thank you for the opportunity to testify today on the anniversary of the 21st Century Cures Act and to update you on FDA's progress in implementing the provisions of this landmark legislation.

The Cures Act gave FDA a broad new set of authorities and resources to adapt our policies and our organizational structure to make sure that our efforts are as modern and transformative as the medical products that we are seeing.

Congress wanted us to have a strong workforce and policies that will enable the America people to capitalize on the breakthrough science that is transforming medicine.

I am proud that my colleagues at FDA have worked hard to meet the commitments under the statute. And I want to commit to you that timely implementation of this legislation is one of my highest priorities. The Cures Act is a defining element of my own policy planning at FDA.

When I arrived at FDA 7 months ago, I remarked that I couldn't imagine a better time to be leading the agency, owing to two important new opportunities. The first were opportunities offered by new science and technology. Gene and cellular therapies, more targeted drugs, regenerative medicine, digital health tools, and new biomaterials offer the potential for dramatically better and even curative therapies for many disorders.

The second were opportunities provided by Congress. The reauthorization of the user fees and, more notably, the Cures Act offer FDA a new platform to fashion these scientific advances into practical treatments for patients. If I came before Congress 5 years ago

and said that within the next 5 years we might have a cure for sickle cell disease or hemophilia or common early stage cancers, such predictions would have been unrealistic.

Such discussions are no longer imprudent. In fact, we should expect these opportunities. While these scientific advances won't be risk-free, these and equally profound clinical opportunities are before us.

The Cures Act inspired a new approach to our work. It was a direction from Congress that you wanted us to think differently when it came to the potential for breakthroughs that could transform human health.

We pledge to remain steadfast to our gold standard for safety and efficacy, but at the same time you asked us to look for ways that we can make our approach to the development of breakthrough products more scientifically modern and efficient to meet the urgent needs of patients.

We have taken the spirit of Cures and set out to extend this directive across our own policymaking and planning. To build on what you asked to do, we will soon release a document that will take full measure of how we are expanding on the provisions of Cures to make sure we are continuing to expand on what Congress set out to achieve.

I want to share with you today one such effort. With the advent of more targeted medicines, we are sometimes able to observe earlier in some cases outsized benefits. This is especially true when it comes to the field of oncology. These situations are compelling us to explore new ways to facilitate and expedite the development and review of these products.

For example, we are currently examining approaches to better expediting review and approval of these products by leveraging FDA's existing expedited programs. Accelerated approval has typically been granted in circumstances where earlier stage or smaller datasets show benefit for a serious unmet medical need. But that showing of benefit is typically based on the drug's effect on a surrogate endpoint. In these cases that endpoint, like tumor shrinkage, is judged to be reasonably likely to predict clinical benefit.

What do you do when we have a targeted drug introduced into a properly selected group of patients which has an outsized benefit on overall survival in a rare or deadly cancer, but where that benefit is seen in a small trial where we would still need more evidence to fully understand how to best use the drug in clinical practice?

We might want to approve such a product earlier and require a post-market confirmatory study to validate the finding, similar to an accelerated approval approach.

Even though the observed benefit in this case is on a clinical endpoint, an early look at survival, and not on a surrogate measure of benefit, we believe using an accelerated approval approach could often be valuable.

Congress clarified our authority under FDASIA to grant accelerated approval based on intermediate clinical endpoints. We want to better define what is meant by intermediate endpoints to ensure that product developers with promising drugs take full advantage

of this provision and can consider it in a broader range of such settings.

As the mechanism of diseases like cancer become more clearly defined and drugs targeting these conditions more carefully tailored to the underlying biology of the disease, we are going to see more such cases, situations where a new drug offers an outsized survival benefit in a selected population of patients in a smaller earlier stage clinical trial.

One reason we want to consider accelerated approval in these setting is that it would include authority to require confirmatory evidence to support the continued marketing of the drug and an expedited withdrawal mechanism if that evidence fails to confirm the benefit. We intend to further explore the application of these principles in additional policy work we are undertaking.

To fully leverage these opportunities and in keeping with the spirit of Cures we are working on a similar proposal. For cancer drugs already approved for one indication, approval for a supplemental application, where the approval concerns a second indication, can sometimes appropriately rely on a more targeted dataset like a single arm study. We intend to issue guidance further clarifying the circumstances in which this is appropriate.

In closing, this may be suitable, for example, when there is a clear and outsized treatment effect and the second indication concerns the same disease as the first one but for on new setting, for example, a targeted drug approved for a third line use that shows benefit in a second line indication.

Cures refashioned and modernized FDA's footprint, enabling new technologies to reach patients more efficiently, giving the agency new authorities and resources to invest in our workforce, and it shapes our spirit of our mission. We will continue to build on its framework.

I look forward to discussing our plans to fulfill and expand on these opportunities, and I look forward to answering your questions.

[The prepared statement of Dr. Gottlieb follows:]



TESTIMONY
OF
SCOTT GOTTLIEB, M.D.
COMMISSIONER OF FOOD AND DRUGS
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE
SUBCOMMITTEE ON HEALTH
HOUSE ENERGY AND COMMERCE COMMITTEE
U.S. HOUSE OF REPRESENTATIVES

IMPLEMENTING THE 21ST CENTURY CURES ACT:
AN UPDATE FROM FDA AND NIH
NOVEMBER 30, 2017

RELEASE ONLY UPON DELIVERY

Chairman Burgess, Ranking Member Green, and Members of the Subcommittee:

Thank you for the opportunity to testify today on FDA's implementation of the 21st Century Cures Act (Cures Act), almost one year after the law's enactment.

The Cures Act was a significant legislative achievement that coincided with a distinctive moment in medicine and technology. This legislation grew out of a bipartisan, bicameral recognition that we are at a moment in science when we have more opportunity to fundamentally alter the course of many human ailments and even cure diseases or reverse the effects of injury and illness.

The Cures Act includes provisions that have the potential to impart far-reaching effects on scientific advancements in medical product development. The new law complements many efforts underway at FDA, all aimed at transforming the way we support product development and marketing authorization and solidifying FDA's gold standard for safety and effectiveness.

Implementation Overview

The Cures Act provides the Agency with important tools that help us continue to meet our mission to protect and promote the public health. As such, it has been a top priority of mine to ensure timely implementation so patients can realize the benefits of this new law. By providing product developers a clear and predictable path for new advances, patients and consumers can realize the benefits of innovations while maintaining confidence that the resulting medical products are safe and effective.

The aim of these policies is to improve patient access to innovative medical products while continuing to protect those who rely on these products. The provisions help FDA in its commitment to continue taking a fresh look at how we regulate products developed through truly novel medical advances to ensure that FDA is encouraging their development and creating efficient, risk-based pathways.

Our implementation of the Cures Act has been integrated into our broader agency efforts. From day one, FDA has worked across medical product centers and offices to fully implement the law and build on its provisions. FDA's headway in pursuing the opportunities enabled by the Cures Act illustrates the Agency's enthusiasm and commitment to the spirit and letter of the law's provisions.

Practically, we have facilitated this through the creation of an intra-agency steering committee to ensure a coordinated approach to implementation. This steering committee, working with subject matter experts in the relevant Centers and offices, helps guide the Agency's timely implementation of the Cures Act provisions. It is led by FDA Office of Commissioner staff ensuring a high-level focus on the implementation of the Cures Act.

The steering committee's first task was to develop the Agency's required work plan to explain the approach we intended to take to implement certain provisions of the Cures Act, both now and in future years. The resulting work plan lays out our vision for the \$500 million in authorized

new funds over nine years, if appropriated, that is included in the law.¹ The steering committee also conducted an analysis of the law's provisions and compiled a list of all FDA-related requirements. The steering committee uses these documents to ensure transparency with the public on our progress by maintaining a website on the Cures Act, as well as a public tracker of deliverables required by the Cures Act. The current tracker lists our commitments and progress towards fulfilling them.² This public information allows a wide range of stakeholders to keep up with our implementation efforts.

We also have worked with our colleagues at the Department and other Health and Human Services (HHS) agencies, such as the National Institutes of Health (NIH), to implement crosscutting provisions. For example, FDA's Office of Women's Health has collaborated with NIH and others on the Task Force on Research Specific to Pregnant Women and Lactating Women to help improve the availability of information available to providers and patients for making evidence-based treatment decisions.

Throughout the implementation process, FDA has utilized our new authorities in the Cures Act to pursue new ways to improve the climate for innovation and advance products to those who need them. In doing so, we have challenged ourselves to look at how we can make the development process more efficient by modernizing our processes and removing obstacles that add to time and cost without meaningfully improving our knowledge about safety and effectiveness.

Implementation Updates

Oncology Center for Excellence

One of our first achievements under the Cures Act was to stand up FDA's new Oncology Center for Excellence (OCE). The OCE marks a shift in FDA's traditional operating structure. It creates cross-center teams to work together to examine products to treat cancer. Rather than focusing on the primary mechanism of action, or on the kind of product platform being used, teams are grouped based on their deep understanding of the disease.

This approach to product review already has had an impact in the setting of oncology—in August, FDA approved the first cell-based gene therapy ever in the U.S. to treat certain children and young adults with B-cell acute lymphoblastic leukemia. A second product to treat adult patients with certain types of large B-cell lymphoma was approved in October. Both products had clinical reviews conducted by the OCE, while our Center for Biologics Evaluation and Research (CBER) conducted all other aspects of review and made the final product approval determinations.

¹ The Cures Act Work Plan can be accessed here: <https://www.fda.gov/downloads/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCA/21stCenturyCuresAct/UCM562852.pdf>.

² The Cures Act Deliverables Tracker can be found on our Cures Act webpage and accessed here: <https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCA/21stCenturyCuresAct/ucm562475.htm#21>.

This is an organizational model that we seek to adopt in other settings. We are evaluating the creation of additional disease-specific offices as part of a more modern approach to the Office of New Drugs (OND) in the Center for Drug Evaluation and Research (CDER). Some of the areas under consideration are immunology and neuroscience. The goals are to provide stakeholders with a single point of contact and to foster synergies and surge capacity across different offices.

Minimal Risk Clinical Investigations

Another cross-cutting initiative has been to produce guidance related to section 3024 of the Cures Act. This section provides FDA with the authority to permit an exception from informed consent for minimal risk clinical investigations when specific criteria are met. Our medical product centers for biologics, drugs, and devices partnered with our Office of Good Clinical Practice and Office of Counterterrorism and Emerging Threats to issue a final guidance related to this provision in July. The guidance will facilitate the conduct of certain minimal risk clinical investigations that are important to address significant public health needs without compromising the rights, safety, or welfare of human subjects.

Regenerative Medicine

One of the most promising new fields of science and medicine is the area of cell therapies and their use in regenerative medicine. These new technologies, most of which are in early stages of development, hold significant promise for transformative and potentially curative treatments for some of humanity's most troubling and intractable maladies.

The Cures Act recognized these opportunities and highlighted the need to establish enhanced pathways for these promising therapies. Immediately after the law passed, CBER moved quickly to establish the Regenerative Medicine Advanced Therapy (RMAT) designation program, as authorized in section 3033. This program aims to facilitate an efficient development program, expedited review of innovative regenerative medicine therapies, and provide more timely access to potentially life-saving products. Products granted designation are eligible for increased early interactions with FDA, including all the benefits available to breakthrough therapies. As of October 31, FDA had granted 11 RMAT designations.

Building on these activities, a few weeks ago, FDA announced the Agency's Comprehensive Policy Framework for Regenerative Medicine. The framework clarifies the Agency's current risk-based, flexible regulatory approach and implements provisions of the Cures Act related to regenerative medicine through a series of two final and two draft guidance documents. When finalized, the draft guidances will further assist in the development of innovative regenerative medicine therapies. The first draft guidance document addresses expedited programs for regenerative medicine therapies products, including the new RMAT designation program, while the other addresses devices used in recovery, isolation, or delivery of RMAT products.

In particular, the draft guidance on expedited programs describes regenerative medicine therapies eligible for RMAT designation as including cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using certain such therapies

or products, as well as gene therapies that lead to a durable modification of cells or tissues (including genetically modified cells). For example, CAR-T products, which represent a durable modification to certain T-cells of their recipients, have been considered by FDA to be a form of gene therapy. Therefore, RMAT designation is available to CAR-T products that meet the other criteria for designation.

CBER is also working to facilitate an effort to coordinate and prioritize the development of standards and consensus definitions of terms to support the development, evaluation, and review of regenerative medicine therapies and regenerative advanced therapies, including with respect to the manufacturing processes and controls of such products. In September 2017, FDA awarded a contract to support the coordination and development of these standards and consensus definitions through a public process, in consultation with the National Institute of Standards and Technology and other stakeholders.

Digital Health

FDA also is working to implement the digital health provisions of the Cures Act. Earlier this summer, FDA released an action plan that included the Agency's precertification pilot program, which explores how to apply a tailored, risk based approach toward digital health technology by looking at the software developer or digital health technology developer rather than primarily at the product. The Cures Act expands on policies advanced by FDA's Center for Devices and Radiological Health (CDRH) and makes clear that certain digital health technologies—such as clinical administrative support software and mobile apps that are intended only for maintaining or encouraging a healthy lifestyle—generally fall outside the scope of FDA regulation. Such technologies tend to be low risk but can provide great benefits to patients and to the health care system by helping keep patients and consumers more informed and engaged in their health. In the coming months, FDA will publish guidance to further clarify what falls outside the scope of FDA regulation and to explain how the new provisions affect pre-existing FDA policies.

In late October, the Agency issued the "510(k) Software Modifications" guidance—the first of several guidance documents clarifying our policy in this space. FDA will also provide guidance to clarify the Agency's proposed position on products that contain multiple software functions, where some functionalities fall outside the scope of FDA regulation, but others do not. In addition, FDA will provide new guidance on other technologies that, although not addressed in the Cures Act, present low enough risks that FDA does not intend to enforce certain pre-market regulatory requirements. Greater certainty regarding the types of digital health technology that are subject to regulation and more clarity on FDA's compliance policies will not only help foster innovation, but also will help the Agency to devote its resources to higher-risk priorities.

Breakthrough Devices Program

While FDA is taking steps to improve efficiency in all our review programs, the Agency is especially committed to helping devices that fill an unmet need move through the process as efficiently as possible. The Cures Act gave FDA new authorities to help achieve this goal. The Agency has issued a draft guidance regarding a new Breakthrough Devices Program, which was created by the Cures Act. Building on our Expedited Access Pathway program, which had been

in place since 2015, the Breakthrough Devices Program is intended to help patients have more timely access to certain devices that more effectively diagnose or treat life-threatening or irreversibly debilitating diseases or conditions, such as technologies with no alternative or that offer a significant advantage over existing FDA-cleared or approved alternatives.

As described in the draft guidance, the program would enable a more agile pre-submission process for breakthrough devices. Breakthrough device innovations that are highly novel can also be more complex to assess. Thus, earlier and more frequent interaction between FDA and manufacturers should allow manufacturers and the Agency to make the best use of resources to bring novel medical technologies to the market more quickly.

510(k) Modifications

Many devices undergo modifications based upon feedback from medical professionals, patients, and other users who help innovators make adaptations to improve a device's performance. A regulatory framework that responds quickly to iteration is key to improving device safety and performance.

FDA finalized two guidance documents on device modifications in October. They are designed to help innovators determine when they need to submit a new premarket notification (510(k)) prior to making a change to a legally marketed device subject to 510(k) requirements. The final guidance documents will help innovators introduce iterative improvements that can improve a product's safety and performance by establishing more predictable, consistent, and transparent criteria regarding when FDA needs to review and clear changes.

These new guidance documents do not change FDA's review standard. Instead, the new guidances enhance predictability and consistency for innovators deciding when to submit new 510(k)s by better describing the regulatory framework, policies, and practices underlying such a decision.

This improved clarity will help reduce the barriers to beneficial innovation and improve patient care by reducing unnecessary submissions to FDA for changes that could not significantly affect device safety or effectiveness, so patients can benefit from enhancements more quickly.

510(k) Exemptions

Under provisions of the Cures Act, FDA exempted more than 70 Class I device types and more than 1,000 Class II device types from the requirement to submit to FDA a 510(k) submission. This Cures directive is part of our ongoing strategy to decrease regulatory burdens on the development of beneficial technologies and reduce the costs of innovation. Device types that are exempt from 510(k) are not generally exempt from other regulatory controls (such as current good manufacturing practice requirements, adequate and proper packaging and labeling, and registration and listing), which ensures consumers can continue to rely on the Agency's oversight of these products while giving FDA more capacity to focus its oversight on higher risk products.

Modernizing Review of Reusable Devices

The Cures Act also provided FDA an important authority to require instructions for use and validation data regarding cleaning, disinfection, and sterilization for certain reusable devices, such as duodenoscopes. In June, as required by the Cures Act, FDA published a list of reusable devices for which the requirement applies, and we believe this will ensure that the premarket requirements for these device types are clear and predictable, facilitating more efficient review of these 510(k)s and safer products for patients.

Least Burdensome Device Review

The Cures Act also expands the least burdensome provisions for device review and requires important least burdensome training for review staff. In fact, even though the Cures Act mandated training only for employees involved in premarket device review, both CBER and CDRH require all medical device review staff to complete least burdensome training because it is integral to how we conduct business. When applied correctly, the least burdensome concept continues to help facilitate the availability of new device technologies without compromising scientific integrity in the decision-making process or FDA's ability to protect the public health. The least burdensome concept continues to be integrated into all device review and other device-related activities, not just select premarket activities.

The Agency also has revised our guidance concerning the proper response to deficiencies in accordance with the least burdensome principles and updated our guidance to incorporate the requirement under the Cures Act that summaries of significant decisions include how the least burdensome principles were applied. FDA also intends to issue in the coming months updated guidance on our overarching principles of the least burdensome concept. This is another instance where FDA is using the authorities under the Cures Act to achieve our objective of making the review process more efficient and ensuring that we are collecting information only when necessary and at the right time during the review process, and without compromising safety and effectiveness.

Patient-Focused Drug Development

In the drug approval space, the Cures Act is facilitating more patient-centered, efficient, and faster drug and biologics development through different mechanisms. We are putting this patient-centered approach at the center of our regulatory activities, which is why we intend to set up a dedicated patient engagement staff in our Office of Medical Products and Tobacco.

The Cures Act emphasizes the need for patient engagement. It directs the Agency to provide information about how it is reviewing patient experience data in reviewing drugs and devices and issue guidance documents to facilitate the collection and review of patient-focused data for drug development. In May 2017, FDA published a five-year plan for issuing these guidance documents.

FDA has already implemented an approach to record and track the submission and review of patient experience data. A new subsection called "Patient Experience Data" is now included in drug and biologic review documents. It will require reviewers to include a brief statement

regarding patient experience data and related information if it is submitted and reviewed as part of an application.

In just a few weeks, the Agency will conduct a public workshop, titled “Patient-Focused Drug Development: Guidance 1 - Collecting Comprehensive and Representative Input.” The workshop is scheduled for December 18, 2017. FDA is holding this public workshop to obtain feedback from stakeholders, including patients, caregivers, patients’ advocates, academic and medical researchers, expert practitioners, drug developers, and others, on considerations for: (1) standardized nomenclature and terminologies for patient-focused drug development; (2) methods to collect meaningful patient input throughout the drug development process, and (3) methodological considerations for the collection of patient data, and the reporting, management, and analysis of patient input. FDA has announced this workshop in the Federal Register and will publish a discussion document before it takes place.

Drug Development Tools

Provisions designed to advance the development and use of drug development tools (DDTs) are some of the most meaningful provisions in the Cures Act. These provisions codify FDA’s role in qualifying biomarkers and other DDTs, that is, determining that a DDT can be used for a particular context of use across different product development programs. Product development tools are critical to efficient, expedited product development.

FDA is establishing a qualification process for DDTs (i.e., biomarkers, clinical outcome assessments (COAs), and animal models) for proposed contexts of use for drugs and biologics. There are similar efforts underway with respect to medical device development tools. FDA must develop a new regulatory process to qualify DDTs to facilitate timely and consistent review of DDT qualification submissions and publicly disseminate information about DDTs under review and following a qualification determination. Once a drug development tool is qualified under this new process, it can be used for its qualified context of use to support regulatory decisions regarding a drug or biologic, including decisions regarding an application for approval or licensure of a drug or biologic or to support the investigational use of a drug or biologic.

To better integrate our work on drug development tools, on August 15, 2017, CDER moved the Biomarker Qualification Program from the Office of Translational Sciences into the Immediate Office of the OND. This places the Biomarker Qualification Program in closer proximity to OND review divisions, fostering improved coordination, scientific understanding, and consistency between biomarkers developed for qualification and those under development as part of drug-specific programs. Similarly, the placement of biomarker and COA qualification programs in the OND Immediate Office enables greater efficiency of operations and greater opportunities for collaborative engagement with external stakeholder communities.

These efforts are already having an impact: the first COA from the COA Drug Development Tool Qualification program has been accepted for review under these updated provisions—the Symptoms of Major Depressive Disorder Scale—and the Agency expects to act on that submission soon. The Scale is a 16-item, patient-reported outcome instrument intended to

capture the patient voice by measuring the symptoms of major depressive disorder that matter most to patients.

FDA has also been active with NIH and other stakeholders in the development of evidentiary criteria to support biomarker qualification efforts. Two recent multi-stakeholder collaborations have been held to help inform future guidance by the Agency, discussing the evidentiary criteria to support biomarker qualification efforts.

Limited Population Pathway for Antibacterial and Antifungal Drugs

The decline in antibacterial drug research and development as serious antibacterial drug resistant infections increase is a critical public health and patient care concern. FDA is working to implement the Limited Population Pathway for Antibacterial and Antifungal Drugs (Limited Population Pathway, or LPAD) provision of Cures to help address this. The Limited Population Pathway allows FDA, at an applicant's request, to approve an antibacterial or antifungal drug, alone or in combination with other drugs, as a limited population drug. This provision builds on ongoing efforts to spur drug development in this area by facilitating the development and approval of antibacterial and antifungal drugs intended to treat serious or life-threatening infections in a limited population of patients with unmet need. In certain circumstances, the Limited Population Pathway will be an important tool enabling FDA to conclude that the benefits of a drug outweigh its risks in the intended limited population.

As required in the Cures Act, FDA is in the process of developing draft guidance describing the criteria, processes, and other general considerations for demonstrating the safety and effectiveness of limited population antibacterial and antifungal drugs. FDA also is familiarizing the scientific and policy community involved in antibacterial drug development with the Limited Population Pathway by mentioning it during public presentations, workshops, and Advisory Committee meetings where development of antibacterial drugs for serious or life-threatening infections is discussed. Additionally, FDA is working with drug sponsors who are interested in utilizing this new pathway by answering questions and providing application-specific information to sponsors when it is requested.

Susceptibility Test Interpretive Criteria

Susceptibility testing is performed in laboratories to determine which antibacterial drugs are likely to be active against the bacteria causing a patient's infection. This information helps healthcare providers to pick an appropriate drug to treat a patient's infection or to determine when additional infection control procedures should be put in place to reduce the chance of spread of resistant bacteria. Before Cures, FDA had a laborious, duplicative process to keep this information up-to-date in drug labeling. FDA is currently working to implement section 3044 of the Cures Act, which clarifies the Agency's authority to efficiently update susceptibility test interpretive criteria, including by leveraging work done by standards development organizations [SDOs], while FDA retains full authority over recognition decisions, and take advantage of tools like the web to modernize how we update susceptibility test interpretive criteria. This allows sponsors of antimicrobial susceptibility testing devices to utilize this information more quickly.

On October 30, 2017, as a first step in implementing this new authority, FDA published a Federal Register notice asking for information to assist FDA in identifying SDOs that meet the statutory requirements in the Cures Act. FDA is working to meet its December statutory deadline to publish the Susceptibility Test Interpretive Criteria website. This website will include FDA's recognition, in whole or in part, of susceptibility test interpretive criteria established by SDOs. More information will be provided about the recognition process when the website is live.

Continuous Manufacturing

Continuous manufacturing—a technologically advanced and automated manufacturing method—provides a faster, more reliable way to make pharmaceuticals. This can help reduce drug shortages and recalls related to problems with product or facility quality.

The Agency is helping to bring continuous manufacturing into widespread use by supporting the pharmaceutical industry's transition to this manufacturing method. With this in mind, the Cures Act allows FDA to issue grants to study continuous manufacturing of drugs and biological products and similar innovative monitoring and control techniques.

During fiscal year 2017, CDER granted an award to the University of Connecticut to develop and build a continuous manufacturing platform with modular components for complex dosage forms, as well as to create a library based on Graphical User Interfaces. These activities support quality-based risk assessment and provide a roadmap to modernize technology and solve continuous manufacturing challenges for complex dosage forms. They also can help the Agency with review processes and provide necessary information to guide policy development. This research is likely to advance the Agency's regulatory science and facilitate production of high-quality, cost-effective complex drug products for the benefit of the public.

Novel Clinical Trial Designs

As technology improves, so does FDA's ability to explore novel trial designs that better fit the needs of researchers and patients. FDA is committed to supporting the use of novel trial designs, modeling, and simulations in drug development and review, to do things like support evidence of effectiveness, optimize dosing, and evaluate adverse event mechanisms.

Building on work that was already underway at the Agency, the Cures Act specifically calls on FDA to assist sponsors in incorporating complex adaptive and other novel trial designs into proposed clinical protocols and applications for new drugs and biological products to facilitate more efficient product development. To do this, FDA is actively planning a public meeting for March 20, 2018. The Agency plans to issue guidance on, among other things, how to use such novel trial designs, how they can help to satisfy the substantial evidence standard, and what are recommended analysis methodologies.

Combination Products

In line with section 3038 of the Cures Act, which addresses the full life-cycle for combination products, the Agency is taking a range of actions to advance the consistency, efficiency,

predictability, and transparency of both the premarket review and postmarket regulation of combination products.

FDA is committed to this work. Leadership of the medical product centers and other appropriate offices sit on the Combination Products Policy Council to guide efforts in the pre- and post-market space. For example, the Agency is currently completing a pilot of a more streamlined intercenter consult process that improves the efficiency of these consultations, an effort that has involved training for over one thousand review staff in the three medical product Centers. Additionally, we are enhancing our training of review staff, such as leveraging prior Agency determinations, to ensure a risk-based approach to regulation of combination products.

FDA is also working to help streamline the process to get these important products to patients. In January, we released final guidance on current good manufacturing practices for combination products, which outlines flexible practices that can be utilized by manufacturers to reduce burdens.

A key provision in the Cures Act calls for FDA's Office of Combination Products (OCP) and the three medical product Centers to work with and provide assistance to medical product sponsors upon request regarding the study design of their product. OCP continues to provide this assistance and has developed a new standard operating procedure for handling these requests to ensure faithful implementation of the Cures mandate.

Real World Data and Real World Evidence

Advances in technology also have the potential to improve the availability and utility of real world evidence (RWE) and real world data (RWD). The Cures Act specifically supports the Agency's evaluation of the potential use of RWE to support the approval of new indications of approved medical products or to satisfy post-approval study requirements for marketed products.

Examples of RWD include data derived from electronic health records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including in-home use settings, and data gathered from other sources such as mobile devices that can provide information about health status. RWD sources (e.g., registries, EHRs, and administrative and healthcare claims databases) can be used as a data collection and analysis infrastructure to support many types of trial designs, including, but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies (prospective and/or retrospective).

The use of RWE and RWD have the potential to allow researchers to answer questions about treatment effects and outcomes more efficiently, saving time and money while yielding answers relevant to broader populations of patients than might be possible in a specialized research environment. This could help streamline clinical development. The use of these data also can help inform the safe and effective use of medical products.

To do this, FDA will establish a program to evaluate the potential use of RWE to help support the approval of a new indication for an already approved drug or to help support or satisfy post-

approval study requirements. Over the past year, CDRH, CBER, and CDER have harmonized their definitions for RWD, data relating to patient health status and the delivery of health care routinely collected from a variety of sources, the clinical evidence regarding the usage, and potential benefits or risks of a medical product derived from analysis of RWD. FDA has already finalized guidance on RWE for devices, and we will issue new guidance to define how we plan to incorporate these principles into product development for drugs and biologics.

FDA's focus on RWE has already advanced patient care. On June 5, 2017, FDA became the first regulatory body in the world to approve the most recent iteration of the Sapien valve, the Sapien 3, to treat high-risk patients whose surgically-placed aortic or mitral bioprosthetic valves were old and worn out. This approval was based in part on data from the Transcatheter Valve Therapy (TVT) Registry, a partnership of the American College of Cardiology and the Society of Thoracic Surgeons. The TVT registry collects clinical data on the performance of transcatheter valve replacement procedures performed in the U.S. once a product goes to market – including both on-label and off-label uses – making it possible, under certain circumstances, to accumulate more data faster, without the need for costly and time-consuming formal clinical trials.

FDA is currently focused on developing a framework for a program that will evaluate the use of real world evidence to support regulatory decisions for new indications or post-approval study requirements. The draft framework, required under the Cures Act, is due in December 2018, but the Agency is already gathering stakeholder input to move this field forward. For example, in September 2017, FDA collaborated on a workshop convened by Duke-Margolis Center for Health Policy to bring stakeholders, including industry, academia, and patient advocacy groups, together to discuss both the challenges and opportunities for applying RWE and RWD to drug development. Similarly, the National Academies of Sciences, Engineering, and Medicine have organized a series of meetings—with FDA participation—to explore these opportunities. The first, also held in September 2017, was entitled “Examining the Impact of Real-World Evidence on Medical Product Development: A Workshop Series.” Two additional meetings are planned.

FDA also is supporting numerous demonstration projects to advance the regulatory framework for how best to incorporate RWE into regulatory decision-making. For example, as part of a big data analytics initiative at the FDA called Information Exchange and Data Transformation (INFORMED), the OCE has a current collaboration with Flatiron Health to examine how RWD can be used to gain insights into the safety and effectiveness of new cancer therapies.

In addition, in June 2017, FDA announced a partnership with CancerLinQ, the American Society of Clinical Oncology's big data initiative. FDA and CancerLinQ will be using real world, aggregate, de-identified patient care data from oncology practices to understand a variety of issues related to the appropriate use of newly approved therapies. The initial focus will be on immunotherapy agents approved for melanoma. FDA is also leading an effort that includes NIH's National Center for Advancing Translational Sciences, National Cancer Institute, National Library of Medicine, and the HHS Office of the National Coordinator for Health Information Technology to develop a general framework by harmonizing several Common Data Models.

FDA will continue to partner with a range of stakeholders to do all the Agency can to address the challenges and realize the opportunities posed by RWE and RWD, so that FDA can get effective treatments and therapies to those who need them more efficiently.

Medical Countermeasures

At FDA, we remain fully committed to continuing to use our authorities to the fullest extent to help facilitate the development and availability of medical countermeasures—such as vaccines, therapies, and diagnostic tests—to counter chemical, biological, radiological, nuclear (CBRN) and emerging threats such as pandemic influenza and Zika virus.

While many of the provisions in the Cures Act that are intended to facilitate the development and availability of medical products in general also will serve to help facilitate the development and availability of medical countermeasures, the Cures Act contains two FDA-specific provisions to help advance the development and availability of medical countermeasures.

Section 3088 of the Cures Act amends FDA's Emergency Use Authorization (EUA) authority (section 564 of the FD&C Act) to permit EUAs that: (1) authorize emergency use of unapproved animal drugs or unapproved uses of approved animal drugs, (2) make applicable other emergency use authorities (e.g., to issue emergency dispensing orders, waive compliance with Current Good Manufacturing Practices, make available CDC Emergency Use Instructions, and extend expiration dates) to approved animal drugs, and (3) allow unapproved animal drugs to be held for emergency use. In January 2017, FDA issued guidance on Emergency Use Authorization of Medical Products and Related Authorities, in which we explained that the Emergency Use authorities and guidance recommendations are now applicable to animal drugs and encouraged anyone interested in utilizing these authorities to contact FDA to discuss how to proceed. FDA plans to address any issues raised as we develop more experience with these new authorities.

Section 3086 of the Cures Act adds section 565A of the FD&C Act for FDA to establish a new priority review voucher (PRV) program to help incentivize the development of material threat medical countermeasures. Upon approval of a material threat medical countermeasure application, FDA will award a PRV provided certain criteria are met. The PRV may in turn be used by the sponsor who receives it, or sold to another sponsor who may then use it, to obtain priority review for a product application that would otherwise not receive priority review. In October 2017, we announced in the *Federal Register* the fee rate for using a material threat MCM PRV for FY 2018 (\$2,830,579; the rate was effective on October 1, 2017, through September 30, 2018). We also plan to issue guidance to address medical countermeasure-specific issues in the near future, with the intent to implement the program consistently with the other PRV programs, such as the Neglected Tropical Disease Voucher Program.

The FDA stands ready to use these new authorities as appropriate to help facilitate the development and availability of medical countermeasures.

Conclusion

These are just some of the ways the Cures Act has supported and enhanced FDA's work to make the process for bringing safe, effective, and innovative treatments to patients more efficient. FDA's improvements in transparency, consistency, predictability, and efficiency will benefit industry, healthcare providers, and, most importantly, patients. We expect our continued implementation of the Cures Act will further advance these goals. The Agency stands ready to work with Congress and stakeholders to help make the promise of the Cures Act a reality.

Thank you for inviting FDA to testify today. I would be happy to answer any questions you may have.

Mr. BURGESS. The chair thanks the gentleman.

The chair now recognizes the Director of the National Institutes of Health, Dr. Collins, 5 minutes for an opening statement, please.

STATEMENT OF FRANCIS COLLINS

Dr. COLLINS. Good morning, Chairman Burgess, Ranking Member Green, other distinguished committee members. It is an honor to be here today with my colleague, Dr. Scott Gottlieb, the FDA Commissioner.

We were cheering a year ago today, November 30, when the Cures Act passed the House of Representatives 392 to 26. And as you well know, this act aimed to catalyze a very important goal shared by all Americans: to speed the pace at which scientific discoveries are translated into lifesaving treatments and cures. And I am here to talk to you today about how that dream is coming true.

We at NIH greatly appreciate your leadership in passing this bipartisan act 1 year ago that enhances our authorities and our resources in ways that will help us to achieve this goal. Many thoughtful provisions are included in the act, such as reducing administrative burdens so our scientists can devote more of their time to research, expanding our ability to award prizes for exceptionally creative ideas, and strengthening measures to protect patient privacy when individuals are involved in research.

In my written statement I have submitted a comprehensive report on how NIH has worked quickly to implement the provisions of the Act. We are motivated by a sense of urgency to help patients in need of breakthroughs. In my oral statement just now, I would like to focus on the Cures Innovation Fund.

Among the vital areas of NIH-supported research being accelerated by this fund are the BRAIN Initiative, the Cancer Moonshot, the Regenerative Medicine Innovation Project, and the Precision Medicine Initiative. I am also delighted to have Max here representing the most important audience for anything we are talking about today, which are those patients who are waiting for answers to conditions that need those answers. And I would also like to recognize my friend Doug Oliver, at the end of the front row, who has been a very effective spokesperson for the importance of investing in regenerative medicine.

Let's begin with the BRAIN Initiative. This pioneering effort is aimed at revolutionizing our understanding of the most complex structure in the known universe, the human brain. In fiscal year 2017, we leveraged our Cures innovation funding with our annual appropriation to launch no less than 110 exciting new brain research projects.

Some of these will develop detailed maps of neural circuits, others will create a census of cell types in the brain, and still others will create powerful new tools to monitor and modulate brain activities. This will advance efforts to develop new ways of detecting, treating, and even preventing many serious brain disorders, such as Alzheimer's disease, Parkinson's, schizophrenia, autism, drug addiction, epilepsy, and traumatic brain injury.

With the help of the Cures Innovation Fund, a second research area, the Cancer Moonshot, is aggressively pursuing a very ambitious goal: to accelerate advances in cancer prevention, diagnosis,

treatment and care, in collaboration with our good colleagues at FDA.

To achieve that goal we must take a variety of innovative steps. These include enhancing the research infrastructure by creating a clinical trials network, with an unwavering commitment today to sharing, to move cancer treatment programs forward rapidly.

In another innovative move, NIH recently joined with the FDA and 12 pharmaceutical companies to launch the Partnership for Accelerating Cancer Therapies, or PACT. This public-private partnership will initially develop biomarkers to speed the development of cancer immunotherapies, an exciting new approach to treatment that enlists a patient's own immune system.

Recently, we have seen some amazing responses from immunotherapy, but we need to bring that kind of success to far more people with more types of cancer and do it quickly. The Cures Innovation Fund, with the support of this Congress, is helping to make that happen.

The Cures Act also provides support for regenerative medicine research. This emerging area of science includes the use of cells and other technologies, such as engineered biomaterials and gene editing, to repair or replace damaged cells, tissues, or even whole organs.

A result of the Cures Act, NIH has launched the Regenerative Medicine Innovation Project. This project recently made eight clinical research awards covering a broad spectrum of science and technology, and going well beyond the funding specifically provided by the Cures Act, because we found it to be so compelling.

Some are focused on common diseases, including diabetes and vision disorders, while others are aimed at rarer conditions, such as sickle cell disease, which Scott has already mentioned is a very exciting time of potentially moving forward to cure in as little as 5 years, and a condition like idiopathic pulmonary fibrosis, and many others.

Also, in partnership with the FDA, we are going to be hosting a workshop next week which is going to explore the state of regenerative medicine research involving adult stem cells. This conference will inform our future research directions by helping us to identify areas of greatest scientific and therapeutic promise.

Finally, I want to tell you how thrilled I am that you supported the Precision Medicine Initiative, PMI, by including an authorization and funding in the Cures Act.

The centerpiece of PMI is the All of Us Research Program, which will enroll 1 million or more Americans from every walk of life. These volunteers will contribute their health data in many ways, over many years, to create a research resource that will catalyze a new era of precision medicine.

This is a truly ambitious goal, and we know that NIH cannot succeed on its own. So all across the nation, NIH is teaming up with the Veterans Administration, health provider organizations, community health centers, and other groups—recently libraries all across the country—to figure out the best ways to recruit participants, especially those that are traditionally underrepresented in biomedical research.

NIH has also partnered with five companies to create a participant technology center, and our partners are testing how wearable devices, like the ones I am wearing today, and many of you are probably wearing something like this, how can we use these to provide easy ways for all of us volunteers to contribute data on physical activity, sleep, heart rates, environmental exposures, and so on.

Getting all these partners on board would have been nearly impossible had not the Cures Act included something called Other Transactions Authority for PMI, making it possible for NIH to move forward with unprecedented speed and flexibility to carry out beta testing of all the many components, and now a planned launch in the spring of 2018.

As someone who grew up in a theater family, I know the value of a dress rehearsal before the curtain goes up. That is what a beta test is. But when it does go up, you and everyone else who supported the 21st Century Cures Act will deserve applause, not just for all of us, but for each of the many, many ways in which Cures supports the work of the National Institutes of Health, or as some have called us, the National Institutes of Hope.

Speaking of hope, let me conclude with a favorite exhortation from the poet Peter Levi: Hope in every sphere of life is a privilege that attaches to action. No action, no hope.

So thank you for your action in enacting Cures. Thank you. I will be happy to answer your questions.

[The prepared statement of Dr. Collins follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Hearing on “Implementing the 21st Century Cures Act:
An Update from FDA and NIH”

Witness appearing before the
House Committee on Energy and Commerce Subcommittee on Health

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

November 30, 2017

Chairman Burgess, Ranking Member Green, Distinguished Members of this Subcommittee, thank you for hosting this important hearing.

More so, thank you for creating the need for this hearing – for the 21st Century Cures Act (Cures Act) which was enacted one year ago. The Cures Act touches on so many important issues. From providing support for four cutting edge research priorities, to enhancing privacy protections to inclusion of various communities in research trials, to reducing administrative burden to expanded prize authority, we at NIH appreciate your leadership and dedication in enacting new authorities to speed the pace of research and improve how science is conducted to transform the way we translate discovery into therapies.

In my testimony, I will highlight how NIH is implementing some of the key provisions of the Cures Act and how it is benefiting the biomedical research community and, most importantly, patients.

Big Data: The Promise of Data Sharing Balanced With the Need for Privacy

As in most fields, computing power is changing the way research is done. The promise of big data cannot be overstated for finding patterns of disease and health and targeting therapeutics to sub-populations. The Congress, in the Cures Act, wisely recognized both the potential and the risks inherent in sharing data sets and NIH has moved quickly to get the appropriate protections in place.

First, on September 7th, NIH issued a Guide Notice to our research community implementing the significant enhancements this Committee made to the Certificates of Confidentiality, making them both automatic and compulsory. To implement this change while minimizing the burden to our researchers, we streamlined the issuance of Certificates into the

terms and conditions of every research award we make involving human subjects.¹ Since October 1st, every NIH award has this added layer of protection for research participants.

Second, on September 17th, guidance on the FOIA exemption for genomic information was disseminated to all NIH FOIA officers.

Only now that the new Cures Act privacy protections are in place, are we moving forward on the exciting new authority to require data sharing. This will be a sea change in biomedical research so we must be deliberate about how to measure the usefulness of data sets, where shared data should be stored, how patient protections are insured, how interoperability is achieved, and what tools researchers most need in the shared environment. On November 6th, NIH made 12 awards in a Data Commons Pilot to answer just these kind of questions. We selected three prominent NIH datasets researchers can use to test their processes. The biomedical research community will be watching this pilot program very closely.

Inclusion

We've made tremendous progress in managing diseases through the development of new drugs and devices over the years that were tested in clinical trials. But trials haven't always included the full spectrum of humanity, and this limits the applicability of study results. It also limits our ability to target therapies and address disparities. Congress helped NIH address this issue through the Cures Act in three focus areas: inclusion of children and seniors; inclusion of pregnant and lactating women; and continuing our focus on women, and racial and ethnic minorities.

¹ <https://humansubjects.nih.gov/coc/index>.

On June 1-2, 2017, as required by the Cures Act, NIH held a workshop on inclusion across the lifespan. It might seem easy to include all age ranges but both children and older adults require special considerations. At the workshop, investigators with expertise in conducting clinical studies with pediatric and older populations, ethics experts, and other stakeholders had a robust discussion about barriers and facilitators to the inclusion of volunteers of all ages in research. The findings and recommendations will be presented at my Advisory Committee meeting on December 14-15, 2017, and we will determine what policy changes are needed to ensure individuals across the lifespan are appropriately included in clinical research.

The Cures Act also asks NIH to continue making progress on the inclusion of women and ethnic and racial minority populations in research. This has been a partnership of the Congress and NIH for many years – the Congress authorized both the NIH Office of Research on Women’s Health and what is now the National Institute on Minority Health and Health Disparities in 1993. With the help of the Congress and the Cures Act, we continue to improve. We are now collecting inclusion data on a study-by-study basis and in the coming year NIH will report, for the first time, inclusion data from studies on a disease and condition basis. At the December meeting, the expert Advisory Committee will have a public discussion of recommendations for further advancing the field and updating our inclusion guidelines. I look forward to the conversation and I will be happy to update you as decisions are made.

Finally, the Cures Act created a Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to advise the Secretary of Health and Human Services regarding gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women.² This area of research is vital, but it is absolutely critical that we carefully

² <https://www.nichd.nih.gov/about/advisory/PRGLAC/Pages/index.aspx>.

consider intentional exposures in this potentially vulnerable time of life. NIH established PRGLAC on March 13, 2017, bringing together federal and non-federal experts, including the Food and Drug Administration, representatives from relevant medical societies, non-profit organizations, and industry, to discuss these important issues.

PRGLAC has already held two meetings – the first on August 21-22, 2017, to determine the scope of current Federal activities on safe and effective therapies for pregnant and lactating women, and the second on November 6-7, 2017, to understand the ethical issues surrounding research to develop therapies for pregnant and lactating women. The third meeting on February 26-27, 2018, will be on communication strategies for health care providers and the public about the use of therapies for pregnant and lactating women, and the fourth meeting on May 14-15, 2018, will be on recommendations to address the gaps in knowledge, ethical issues, and communication strategies for therapies used by pregnant and lactating women.

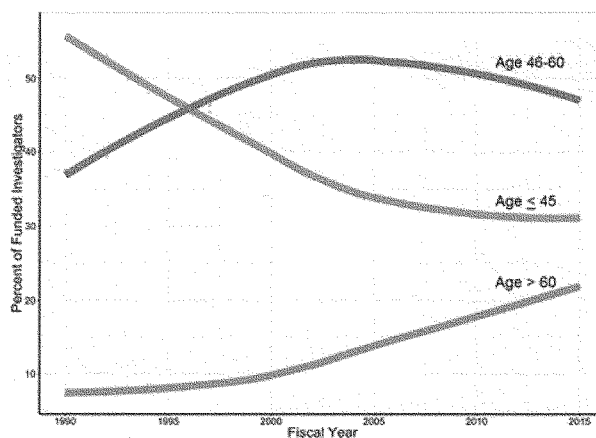
Based on the outcome of the Task Force meetings, a report with recommendations will be developed for the HHS Secretary. NIH is grateful to the Congress for recognizing the need for careful consideration in this area of research and looks forward to addressing any recommendations made by the Task Force.

Strengthening Biomedical Workforce

NIH and its stakeholder community have for many years been concerned about the long-term stability of the biomedical research enterprise. As a consequence of NIH's loss of more than 20 percent of its purchasing power from 2003 to 2015, researchers were forced to vie for limited resources, leading to a hypercompetitive environment. With success rates below 20 percent, many highly meritorious applications continue to go unfunded. This has too often

resulted in misaligned incentives and unintended consequences for talented researchers at all career stages who are trying to succeed and stay in science. The current environment is particularly challenging for many new- and mid-career investigators.

Over the last several years, NIH has taken numerous steps to balance, strengthen, and stabilize the biomedical research workforce, but these measures have only taken us so far. While the percentage of NIH awards that support early-career investigators has gone from declining to flat, these gains have been offset by a decline in the percentage of NIH awards that support mid-career investigators.



As a direct result of the Cures Act, in June 2017, NIH launched the Next Generation Researchers Initiative³ aimed at strengthening the biomedical workforce with a focus on early career investigators or investigators who are at an early stage in their career. NIH intends to take a multi-pronged approach, which we outlined in an article published on November 7, 2017,⁴ to

³ <https://grants.nih.gov/ngri.htm>.

⁴Michael Lauer, Lawrence Tabak, and Francis Collins, "Opinion: The Next Generation Researchers Initiative at NIH," *PNAS*, 114 (2017): 11801-11803.

increase the number of NIH-funded early-stage and mid-career investigators and to stabilize the career trajectory of scientists.

NIH will develop evidence-based, data-driven strategies to assure that NIH investments are directed in ways that maximize scientific output. Institutes and Centers will also place greater emphasis on current NIH funding programs to identify, grow, and retain new- and mid-career investigators across these critical career stages. The NIH Office of the Director will track progress across ICs and assess if these strategies are working. I am personally committed to this issue and thank the Committee for their support of early- and mid-career investigators.

System Innovation: Reducing Administrative Burden and Increasing Efficiency

Policies generated with the best intentions sometimes have serious adverse consequences for research. The Cures Act included numerous provisions that cut the bureaucratic red tape that slows the progress of science. It also provided NIH with new authorities to improve efficiencies and speed up the discovery process.

The Cures Act included provisions to improve ClinicalTrials.gov. ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world that plays a crucial role in ensuring the transparency and accountability to the public of researchers and their sponsors. In addition, this resource is used by researchers to stay up-to-date on developments in their field, find collaborators, and identify unmet needs, and it is also used by patients and families to search for potential studies to enroll in or learn about new treatments that are being tested. NIH strives to make this resource as user friendly as possible so it can benefit researchers, patients, and their families, and the Cures Act is helping in several ways.

First, the Cures Act made technical fixes to the legislation establishing ClinicalTrials.gov that ensure NIH is able to capture more clinical trials in the system and improve our oversight and transparency. Second, it required NIH to consult with relevant Federal agencies and other stakeholders to receive recommendations to enhance ClinicalTrials.gov's usability, functionality, and search capability. In February 2017, the National Library of Medicine (NLM), along with 18F, a digital services consultancy within the General Services Administration, began conducting user research on ClinicalTrials.gov with a range of stakeholders. As a result of this work, NIH rolled out a first in a series of changes to ClinicalTrials.gov on June 19, 2017. On September 25, 2017, NLM released more updates as the next phase in its ongoing effort to enhance the functionality of the database. In response to the Cures Act, NLM will work continuously to make it easier for users to find and participate in clinical trials.

In an effort to improve efficiency, the Cures Act provided a new EUREKA prize authority and allowed NIH to use Other Transactions Authority (OTA) in two areas that need extra flexibility and collaboration: the Common Fund and the *All of Us* Research program, part of the NIH Precision Medicine Initiative.

The EUREKA prize authority is being implemented in three ways:

- On November 2nd, the National Institute on Aging issued a request⁵ for public input on (1) the feasibility of three potential prize competitions focused on Alzheimer's disease (AD) and related dementias (ADRD): Validating predictors of AD progression; PET radiotracer to measure in vivo synaptic integrity; and low cost innovation of improving systems of care for AD/ADRD patients and caregivers; and (2) any other suggestions on

⁵ <https://grants.nih.gov/grants/guide/notice-files/NOT-AG-17-018.html>.

AD/ADRD research goals to connect to a prize. Comments are due on December 31, 2017.

- NIH formed the EUREKA Prize Coordination Committee to review future proposals for future EUREKA prize competitions.
- NIH funded the National Academy of Sciences (NAS) to study Innovation Prizes and Federal R&D with specific emphasis on strategies to determine which “EUREKA” prize topics are consistent with congressional intent. The NAS study will also consider the strengths and weaknesses of various measures of health outcomes and effects on government expenditures. The NAS intends to hold a workshop in 2018.

OTA is integral to our exploration of how best to structure data sharing, known as the Data Commons Pilot Phase,⁶ which was announced on November 6th. The goal of the NIH Data Commons is to accelerate new biomedical discoveries by providing a cloud-based platform where investigators can store, share, access, and compute on digital objects (data, software, etc.) generated from biomedical research and perform novel scientific research including hypothesis generation, discovery, and validation. The use of OTA awards allows flexibility for the awardees to work together to design innovation solutions that meet the computational and scientific needs of the Pilot.

The *All of Us* Research Program aims to enroll one million individuals in a decades-long research project. That ambitious goal requires flexibility, complex and dynamic interactions, and ways to engage non-traditional NIH awardees to advance the mission. For example, *All of Us* has used OTA to make awards to the Healthcare Provider Organizations to help build the

⁶ <https://commonfund.nih.gov/bd2k/commons/awardees>

research protocols, test enrollment procedures, and collect essential health data and biological specimens.

The Cures Act also recognizes that two of the cornerstones of scientific advancement are rigor in designing and performing scientific research and the ability to reproduce biomedical research findings. In recent years, the scientific community has become aware of the need to improve rigor and reproducibility. In 2014, NIH worked with scientific publishers to develop a set of principles and goals that 79 publishers have now endorsed. As the Cures Act requires, my Advisory Committee has convened a Working Group on Rigor and Reproducibility and they are reviewing the experience of the last few years, leading to the development of recommendations for a formal policy. I look forward to updating you as this effort takes shape.

NIH Innovation Fund

Last, but certainly not least, the Cures Act provided multi-year funding through the NIH Innovation Fund for four highly innovative scientific research initiatives: the Precision Medicine Initiative (PMI), the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, the Cancer Moonshot, and the Regenerative Medicine Innovation Project. As required by the Cures Act, on March 28th, I solicited recommendations from my Advisory Committee on how to allocate the funds. We had a robust conversation about each of the initiatives and the Advisory Committee members provided critical advice on how to move forward. As a result of that discussion, and conversations with my NIH colleagues, we drafted the NIH Innovation Fund Work Plan,⁷ which was submitted to Congress in September 2017, outlining how the agency will use the NIH Innovations Funds for each of these four initiatives. I

⁷ <https://www.nih.gov/sites/default/files/research-training/initiatives/nih-cures-innovation-plan.pdf>.

would like to tell you a bit about each of these initiatives and how the NIH Innovation Funds are helping to move each initiative forward.

The Precision Medicine Initiative

Precision medicine is a revolutionary approach for disease prevention and treatment that takes into account individual differences in lifestyle, environment, and biology. While some advances in precision medicine have been made, the practice is not in use for most diseases. The *All of Us* Research Program, a key element of PMI, is building a national resource—one of the world's largest, most diverse biomedical data sets in history—to accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care. *All of Us* will engage one million or more U.S. volunteers from all life stages, health statuses, races/ethnicities, and geographic regions to reflect the country's diverse places and people to contribute their health data over many years to improve health outcomes, fuel the development of new treatments for disease, and catalyze a new era of evidence-based and more precise preventive care and medical treatment.

Across the nation, NIH has engaged 10 large health provider organizations, six community health centers, and the Veterans Administration to be our partners in this ambitious study. The program is launching in stages. The beta phase began in May 2017 during which each of our partners are testing their systems and processes to ensure a good experience for participants.

In July 2017, the program made its first four community partner awards to motivate diverse communities to join and remain in the program, with a focus on those traditionally underrepresented in biomedical research. Each of these organizations has deep, trusted

relationships within and ties to their communities, and we are so very pleased to have the opportunity to partner with them to enhance our outreach into communities that have traditionally been underrepresented in biomedical research. NIH has also engaged with organizations to create mobile apps to enroll, obtain consent from, collect data from, and communicate with *All of Us* participants. One of our partners is working with FitBit on a pilot that will start in mid-2018 to test out ways for participants to easily and efficiently contribute data on physical activity, sleep, heart rates, and other behavioral health information.

We anticipate to roll out nationally in spring 2018. Following the national launch, we will make continuous improvements and updates to the program based on participant feedback and emerging scientific opportunities and technological advances. The Cures Act Innovation Funds will be critical to ensuring the success of *All of Us* and the promise of personalized medicine.

The BRAIN® Initiative

The BRAIN Initiative is aimed at revolutionizing our understanding of the human brain, the most complex structure in the known universe. Launched in 2013, this large-scale effort will push the boundaries of neuroscience research and equip scientists with insights necessary for treating a wide variety of brain disorders. By accelerating the development and application of innovative technologies, researchers will be able to produce a revolutionary new dynamic picture of the brain that, for the first time, shows how individual cells and complex neural circuits interact in both time and space. Long desired by researchers seeking new ways to treat, cure, and even prevent brain disorders, this picture will fill major gaps in our current knowledge and provide unprecedented opportunities for exploring exactly how the brain enables the human body

to record, process, utilize, store, and retrieve vast quantities of information, all at the speed of thought.

NIH leveraged the Cures Act's FY 2017 Innovation Funds, in addition to our annual appropriation, to launch 110 exciting new research projects.⁸ These projects are focused on developing detailed brain circuit maps and powerful new tools to monitor and modulate brain activity in animal models to benefit patients with neurological and psychiatric disorders. Understanding the way the brain processes information and how it lays down memories and retrieves them will be instrumental for understanding brain health, and ultimately, preventing brain disorders such as Alzheimer's disease, Parkinson's, schizophrenia, autism, drug addiction, and traumatic brain injury. These awards add to work already underway to give us a high-resolution picture of the circuits and networks in the brain, how they work, and where they can go wrong.

The Cancer MoonshotSM

The Cancer Moonshot,⁹ funded in the Cures Act, has an ambitious goal: to dramatically speed advances in cancer prevention, diagnosis, treatment, and care. The National Cancer Institute (NCI) solicited direct input from the public and convened a Blue Ribbon Panel (BRP) of the nation's top cancer researchers, oncologists, patient advocates, and private-sector leaders. In September 2016, the BRP presented its report outlining ten ambitious and achievable recommendations to the NCI's National Cancer Advisory Board. These recommendations shape the scientific blueprint of the Cancer Moonshot representing areas of research that are poised to

⁸ <https://www.braininitiative.nih.gov/funding/fundedAwards.htm>.

⁹ <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative>.

accelerate our understanding of cancer and bring benefit to patients. Overall, the recommendations create a vision for future cancer research and treatment in which:

- Researchers can identify possible targets for the development of new cancer treatments and preventive interventions, including immunotherapy and immunoprevention, and learn more about how to avoid or overcome cancer drug resistance in patients;
- Diverse groups of patients contribute information about their cancer, obtain a genomic profile, learn what treatments might work best given their profile, and identify clinical trials that may be appropriate for them;
- Infrastructures are established so that health care providers and researchers can share, access, and analyze information that improves the understanding of how tumors evolve, better predicts treatment outcomes, and helps control patient symptoms and side effects.

Some of these goals are scientific in nature, and some are systemic. If we are to speed advances, we cannot simply do more of the same. We must transform the way we conduct research, the way we share results, and the way we get discoveries into patient care. In FY 2017, NIH made 142 Cancer Moonshot awards, including efforts to leverage advances in immunotherapy, understand drug resistance, and develop of new technologies to characterize tumors and test therapies. These national and international collaborations will drive discovery for cancer patients and their families. I would like to highlight one of those collaborations for you today.

On October 12, 2017, NIH and 11 leading biopharmaceutical companies launched the Partnership for Accelerating Cancer Therapies (PACT), a five-year public-private research

collaboration totaling \$215 million as part of the Cancer Moonshot.¹⁰ PACT will initially focus on efforts to identify, develop, and validate robust biomarkers — standardized biological markers of disease and treatment response — to advance new immunotherapy treatments that harness the immune system to attack cancer. We have seen dramatic responses from immunotherapy, often eradicating cancer completely for some cancer patients. We need to bring that kind of success — and hope — to more people with more types of cancers, and we need to do it quickly. A systematic approach like PACT will help us to achieve success faster.

With the support of the Congress, the Cancer Moonshot will transform the way cancer research is conducted and ensure that substantial progress is made for patients and their families.

The Regenerative Medicine Innovation Project

Regenerative medicine is an emerging area of science that holds great promise for treating and possibly even curing a variety of injuries and diseases. Regenerative medicine includes using stem cells and other technologies, such as engineered biomaterials and gene editing — to repair or replace damaged cells, tissues, or organs. Stem cell-based approaches are under development in labs around the world, and some have already moved into clinical trials. Such progress notwithstanding, much work remains to be done toward the development of safe and effective regenerative medicine interventions to realize the full potential of this field.

As a result of the Cures Act, NIH launched the Regenerative Medicine Innovation Project to support clinical research on adult stem cells while promoting the highest standards for carrying out scientific research and protecting patient safety. The \$2 million Cures provided for

¹⁰ <https://www.nih.gov/news-events/news-releases/nih-partners-11-leading-biopharmaceutical-companies-accelerate-development-new-cancer-immunotherapy-strategies-more-patients>.

this initiative in FY 2017 were amplified through matching funds and NIH Institute contributions to reach a total of just under \$5 million. In September, NIH made eight clinical research awards¹¹ that cover a broad spectrum of science and new technologies, and have the potential to advance understanding and treatment of common diseases – including diabetes, anemia, corneal and other eye diseases, and chronic skin ulcers – as well as rare diseases, including idiopathic pulmonary fibrosis, inherited skin diseases, and sickle cell disease.

Several awards will explore the use of adult stem cells to make specialized cells and tissues that could help reduce the need for whole organ transplants or otherwise restore normal function. Others aim to develop reliable methods of generating red blood cells and platelets in the lab to improve the safety and supply of blood available for transfusion.

NIH looks forward to the opportunity the Cures Act provides to advance this field of science and is hosting a workshop on December 6-7, 2017,¹² to explore the state of regenerative medicine science involving adult stem cells, with a focus on approaches for the development of safe and effective products. This will help inform our funding decisions in future fiscal years.

Conclusion

Thank you for your leadership and dedication that resulted in enacting the Cures Act one year ago. Over the past year, the Cures Act has provided NIH with critical resources and tools to advance our mission – to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness

¹¹ <https://www.nih.gov/rmi/fy-2017-funded-awards>.

¹² <https://www.nih.gov/research-training/medical-research-initiatives/cures>.

and disability. We appreciate Congress's support for NIH through the Cures Act and will continue to implement the law to accelerate scientific discoveries and benefit patients.

Mr. BURGESS. The chair thanks both of our witnesses for their testimony, and we will move into the member question portion of the hearing.

I actually want to recognize the chairman of the full committee, Mr. Walden from Oregon, for 5 minutes.

Mr. WALDEN. I thank the chairman.

And again thank you both, not only for your good work, but also your terrific testimony here today.

And I also want to thank Dr. Gottlieb for his excellent efforts to make sure that our warfighters have access to cutting-edge medical devices and medicines that are both effective and safe for them. We appreciate the work you did with us and our friends at the Armed Services Committee and Pentagon to get that done.

Dr. Gottlieb, the FDA Oncology Center of Excellence was created in Cures as a model of how collaboration in science among and within government agencies should be done in the future. This is a new model, and I know we were hoping here in Congress that this would succeed. And in your testimony you reference the role of OCE in the review and approval of two cell-based gene therapies that are indicated for treatment of cancer patients.

Can you speak a little bit more about how groundbreaking these two treatments are and the role OCE played in their approval?

Dr. GOTTLIEB. Thank you, Mr. Chairman.

I just want to make one brief comment about the legislation that this committee helped craft and crafted with respect to the warfighter. I think it is going to give us a profound opportunity to expedite the approval of products destined for the battlefield setting and to help protect and promote the health of warfighters in the battlefield setting.

We look forward to early implementation of that and robust implementation of that. We will try to make an effort early on to put out specifications on how we plan to make full use of that. I think it is going to provide a profound opportunity for our warfighters, and I thank the committee.

With respect to the Oncology Center for Excellence, the products that you refer to were gene therapy products that we think are going to represent sort of a transformative opportunity as a class of products for the treatment of patients with a range of conditions, including cancer. These were CAR-T products where cells are genetically altered to attack cancer and personalize to the patient's individual cancer.

With respect to the Oncology Center for Excellence, it was instrumental in the review of these products. We believe that the orientation for the future across the entire agency is to try to consolidate the clinical portion of the review among the agency's various medical product centers.

We divide medical products into different centers, but the clinical aspects of the review remain the same, even if the product features are different. And so trying to consolidate that clinical portion of review provides a lot of efficiency, rigor, and also helps quicken the process. And so standing up this new oncology center we think is critical to the future of these classes of products.

Mr. WALDEN. Thank you, sir.

Dr. Collins, over the last several years NIH has been acting to address a biomedical research workforce that is tilted toward, frankly, late-career investigators. The population of grant recipients is highly concentrated, with 10 percent of NIH-funded investigators receiving over 40 percent of NIH funding.

Analyses conducted by your agency and others have shown that a more diverse population of NIH grant recipients would be beneficial to biomedical research. Cures required the NIH to develop strategies to promote and facilitate the next wave of young researchers, and in your testimony you talk about the Next Generation Researchers Initiative.

Can you further elaborate on the multipronged approach you plan to take to increase the number of NIH-funded early stage and mid-career investigators.

Dr. COLLINS. Thank you for the question. This is an area of great and high priority for us, and we appreciated very much the way in which the Cures bill called this out and gave us additional encouragement to think boldly about how we can be sure this next generation of researchers are getting their start as independent investigators with all of the energy and creativity that they bring to it.

And we could look at our own demographics and see that we were increasingly seeing an aging of our workforce. And while we have many investigators who are highly productive as senior investigators, we were worried that the next generation was having a tough time coming on board.

So over the course of this past year since the Cures Act passed, and guided by many conversations before that, we have come up with an approach which is going to provide additional resources for those who come to us for the first time with a grant that has not previously been funded by NIH, but this is their start, and to provide additional opportunities for those individuals, if they fall in the top 25 percent of applicants, to be able to receive funding.

We made this decision fairly late in fiscal year 2017, but we were determined to go ahead and implement it. We are still in the process of identifying all of those investigators who were reviewed in fiscal year 2017 that otherwise would have missed the cut, but whom we now believe we can reach down to and find funds for.

And we are also very concerned about those who are at risk of losing all of their funding. They got started into the pathway, they came back for their competing renewal, just missed the cut, and without that they may have to close their labs and do something else. We are also seeking then to identify those individuals and give them an additional boost.

Now, that money has to come from somewhere, and that means that we may not be able to be quite as generous in other areas of research, including some labs that are extremely well-funded, and as you can imagine, not everybody has been excited about that part.

But we do believe it is the right thing to do. This is the future. If our mission is to try to find every place that we can to use the dollars that the Congress provides us to get the maximum benefit, those young investigators just getting started are a critical part of that.

Mr. WALDEN. Thank you.

Thank you both for the good work you are doing and for being here today before the committee.

With that, Mr. Chairman, I yield back.

Mr. BURGESS. The chair thanks the gentleman. The gentleman yields back.

The chair recognizes the gentleman from Texas, Mr. Green, 5 minutes for questions, please.

Mr. GREEN. Thank you, Mr. Chairman.

Over the last decade there has been a growing recognition in the U.S. and abroad that antibiotic resistance poses a serious and growing threat to our health. Antibiotics are the underpinning of modern medicine. Without them important medical advances such as chemotherapy and surgeries become very risky because of the possibility of infection.

Addressing this threat requires a multipronged approach, including reducing the inappropriate use of antibiotics in human healthcare and agricultural settings and developing new antibiotics and other therapies. We know that there are a number of challenges in discovering and developing new antibiotics.

Dr. Collins, my first question. There are basic scientific barriers which impede new antibiotic discovery and development. Can you tell us what the NIH is currently doing and will be doing to address these barriers?

Dr. COLLINS. We have a very important role to play. So thank you for the question.

Yes, there have been challenges in terms of keeping this pipeline of discovery and development going for antibiotics, in part because some sort of looked at this as a bit of a market failure because of the expectation that new antibiotics would have potentially a very limited market for a while. You would want to save them for those circumstances where you really needed them.

So NIH has an even larger role to play in this space in terms of the discovery part and in moving the new discoveries along the pipeline closer to commercialization, to de-risk those projects, so that antibiotics will be seen by the commercial sector as something that they are ready to pick up and go. And we at NIH, particularly through the National Institute of Allergy and Infectious Diseases, led by Tony Fauci, have a very significant amount of funding invested in this space.

There have been some exciting developments. One is basically using new technologies to discover naturally occurring antibiotics that are created by soil organisms that we didn't previously know were there because we can't culture them in the lab, but new technologies have made that possible. There is a whole new generation of ideas coming from there.

But this is not a solved problem. I am glad you are raising it. It is going to take the full effort of the public and the private sector, supported by this Congress, to be sure that we are inspiring the maximum energy in this space, because we have a ticking clock here for a significant number of individuals who are being found with infections for which none of our antibiotics currently would be able to work.

Mr. GREEN. Well, we will not be able to succeed in the goal of developing antibiotics without a strong bench of scientists. What is

NIH doing to ensure that these young scientists are pursuing careers in the antibiotic discovery and development?

Dr. COLLINS. Well, this ties into the answer I gave a moment ago to Chairman Walden about the things that we are doing to try to encourage our first-time investigators to come on board and to be able to get successfully funded. And in fact many of those investigators are in this area of infectious disease. So as we are lifting all the boats for that category of investigators, we are also helping in this space.

But the National Institute of Allergy and Infectious Diseases also, because this is a high priority, issues special funding announcements, specifically recruiting investigators to work in this space, recognizing that there are people out there who might just work on something else, but knowing that there is a funding opportunity, would raise their hands and say, let's work on this. And we have to do all those things together.

Mr. GREEN. Dr. Gottlieb, this committee has taken the threat of antibiotic resistance very seriously. In 2012, Congress passed the Generating Antibiotics Now Act, the GAIN Act, which our former colleague, Phil Gingrey, who is here today. It came out of this committee and gave exclusivity to new antibiotics to treat serious and life-threatening infections.

Just last year in Cures we passed the ADAPT, which created a new regulatory pathway for antibiotics that treat serious and life-threatening infections and meet an unmet need. I thank Congressman Shimkus for picking up that, cosponsoring. Can you give us a status update on implementation of ADAPT?

Dr. GOTTLIEB. It continues to move forward.

I will comment on a couple things, if I may, Congressman. To answer, to pick up an earlier comment you made, we are going to continue to take steps to try to reduce antibiotic use in veterinary animals. We have taken steps, as you know, to put them under veterinary supervision. And we are going to look at continued steps we can take to address some of the prevention claims in those labels and build on the good work that was begun by my predecessor, Dr. Hamburg.

Another important provision—you mentioned the GAIN Act—another important provision is obviously the LPAD designation that was created by the Cures Act. We are going to put out guidance on that this summer. We have had a limited number, but a robust number given the early days of pre-IND meetings with sponsors that are looking to take advantage of that provision as a way to accelerate the approval of products targeted to resistant organisms.

So I want to thank the committee for the collective good work that you have done through all of this legislation. This has been immensely important to the agency in giving us a new set of tools to address these issues.

Mr. GREEN. Thank you. And I don't have any more time left. But, again, thank you for that effort.

And thank both of you for being here today and the work you are doing. And, obviously, as a committee we want to continue to partner with you.

Mr. GUTHRIE [presiding]. Thank you. The gentleman's time has expired. And I will recognize myself for 5 minutes for questions.

Thanks, Dr. Collins, Dr. Gottlieb, for being here.

When I am home a lot of times doing townhalls or whatever, a lot of times most of the things I talk about is what is happening from this subcommittee in the healthcare world and the research. It is just fascinating stuff that is going on. As Dr. Gottlieb said, we are talking about being able to hopefully be on the cusp of curing diseases we never thought about.

I remember about this time last year the roundtable where Roger Daltrey was here. He was talking about teenage cancer. We also had a young man who was talking about cystic fibrosis. And I have a friend who lost his son in his mid-twenties to cystic fibrosis.

So I was sitting there thinking about, wow, he is young, my daughter's age, and where we were a few years ago he probably had just a few years left to live. And depending on a lot of circumstances, but they talked about he may live a full life expectancy. And that is really what is happening with the research at NIH, what is happening in the private sector.

And so I think for me what made 21st Century Cures exciting—and all of us have these experiences—I had a constituent whose son has Duchenne—or a constituent that has it—his father that has Duchenne Muscular Dystrophy, who would come to our office and say, “There is this promising trial. My son is not in the trial. But it doesn’t improve you, but it prevents you from regressing.” So he was racing against time for his son not to get into a wheelchair, because his goal was for his son not to be in a wheelchair.

Another one, a constituent called crying whose son was on the trial for the artificial pancreas. And then the trial was over. Of course, it was in a lab setting, so they couldn’t take it home. And she said, “My son has never felt this good since he was diagnosed, and now I have got to give this up. They have it back now because it has been approved.”

And I felt that because I had a child with little childhood issues, and parents immediately become experts in the information around that childhood disease, it just drives your life, I can tell you that.

And so we hear from a lot of people, and what we want to be able to say with confidence is that the money we are appropriating has been spent correctly, which I feel confident with your leadership at NIH.

And, Dr. Gottlieb, we want to make sure that the FDA is doing everything to get these.

Because if you are a parent and you are not in the clinical trial, but you are hearing that, “Well, this is for a small basis, but we are not sure I can extrapolate along the whole population,” You want it for your child if you can have it, but understand the safety and the efficiency that you guys have.

And so what we wanted to do, my view of what 21st Century Cures is all about, how do we give you the tools in your research and in your approval process to make sure that people in those situations are confident that it is coming as fast as possible, if we have to accelerate the approval process in those things moving forward.

And so I am excited for this overview, because I think this is an example—we have Mr. Upton and Ms. DeGette, who were the co-sponsors, 392 to 20-something I think was the count—that it is

something that drives all of us here in Washington, because we all these experiences personally or with our constituents.

And the one area that I focused on, and it was the continuous manufacturing, that is kind of my background. So, Dr. Gottlieb, I appreciate you being here. And I understand the development of continuous manufacturing systems could be some of the most significant developments in the pharmaceutical industry in the next decade. And I am happy to hear that FDA is taking steps to facilitate progress in this arena so that our country can recognize the benefits of this faster, in a more reliable way to manufacture pharmaceuticals.

Can you speak to the next steps in this arena? And will you be providing additional grants? And how do you envision this technology improving in the field?

Dr. GOTTLIEB. Thank you for the question, Congressman.

As you know, this committee provided us a good head start in trying to facilitate the continued development of this very important technology, as you rightly noted, providing grants for the development of tools that will help this technology continue to advance.

We have allocated one such grant of I believe a million dollars. We have about \$4 million left to allocate, we are going to do that, to look at other programs, mostly in academic institutions, that can help facilitate the development of the regulatory tools that we will use to better evaluate and allow this technology to advance.

This is very important, you mentioned, to allowing more efficient, maybe lower cost development or manufacturing. It also is very important to trying to address drug shortages. Because of the nature of continuous manufacturing you don't have as much risk of discontinuities in the manufacturing process as you would through traditional manufacturing.

And the final point I would make is that by using continuous manufacturing you require a much smaller, less expensive footprint. So I think that the rapid deployment or the further deployment of this technology is going to lend itself to potentially repatriating some of the manufacturing that we have seen go offshore coming back to the United States.

And a final thought is that I think this technology is going to be very important to some of the newer, more complex products that we see in development, like gene therapy. So we think of continuous manufacturing with respect to small molecules. It is also being adopted with respect to biologics as well.

Mr. GUTHRIE. Well, thank you. As I said, as my friend's son with Duchenne, they are racing against time, so speed is important. But the regulatory side is important, too, as I understand that, as well.

My time has expired. I would like to recognize the ranking member of the full committee, Mr. Pallone, for 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman. You already actually asked one of my questions, so I have to cut that out.

But let me start out with Dr. Collins, and then I will go back to Dr. Gottlieb about continuous manufacturing, if I could.

Dr. Collins, during the 21st Century Cures debate we had a lot of discussion about the future of the biomedical research workforce and its importance to the U.S. remaining the world leader in bio-

medical innovation. While I am glad that we are able to work together to advance policies that support the development of the next generation of researchers, I am concerned about reports on how the House tax bill could thwart such efforts.

As you know, a fundamental element in pursuing careers in biomedical research is obtaining a graduate degree. Unfortunately, the House tax bill could put such education out of reach for students. According to my own Rutgers University president, Dr. Robert Barchi, the provision of the House tax bill that would tax as income tuition that schools waive for graduate students working as teaching or research assistants, would impose—and this is a quote from the Rutgers president—would impose an especially heavy burden on our graduate students, many in STEM fields. Other college leaders have said that the change will make graduate education unaffordable, lead to fewer graduate students at time when the U.S. needs more student-earning advanced degrees in the STEM fields to remain competitive.

So I just wanted to ask you, are you worried that making tuition waivers taxable income for graduate students would harm our efforts to create the next generation of scientists? And how might such a result harm our ability to advance the discovery and development of new treatments in Cures, which of course was the galvanizing force behind 21st Century Cures, if you would?

Dr. COLLINS. Congressman, thank you for the question, and it ties in with what I was saying a few minutes ago responding to Chairman Walden about the Next Generation Researchers Initiative, which we are putting a lot of time and effort into trying to be sure becomes a high priority.

Certainly graduate students as the path toward those independent investigators of the future are absolutely critical, and we want to have all the best and brightest who are interested in pursuing those careers to have the opportunity to do so. And anything that represents a major impediment in that regard is something we should take with great seriousness.

I am not an expert in tax reform or in the particular provisions of any of the bills that are under consideration, but certainly I think we can all agree that given that science has driven our economy in this country—by most estimates more than 50 percent of our gross since World War II has been on the basis of science and technology—this is a very important area for continued investment. And anything that would diminish the interest and the talent of the next generation in joining that workforce is something we should be very cautious and careful about.

Mr. PALLONE. I appreciate that. Thank you.

So let me go back to Dr. Gottlieb. I know that Mr. Guthrie talked about the continuous manufacturing issue. And you mentioned, I think, Dr. Gottlieb, that you awarded the first continuous manufacturing grant in this fiscal year, I guess to the University of Connecticut, to build a manufacturing platform for complex dosage forms.

What I wanted to ask though is, will you discuss further how many additional grant awards the agency intends to offer and what criteria the agency is considering when awarding these grants for the continuous manufacturing?

Dr. GOTTLIEB. Thank you for the question.

I mentioned we had \$5 million to allocate. We allocated a million dollars of it and we are going to continue to allocate the other \$4 million. I am not quite certain how many different grants we will give, but there will certainly be a number of grants awarded. And there are a number of academic institutions doing good work in this area, including one in my hometown of Rutgers University, that has a program looking at this.

The criteria we look at are programs that are developing regulatory tools that can serve as the basis for how we are going to evaluate this technology when sponsors bring in applications where they are employing continuous manufacturing. So because it is so novel, it requires us to think differently about how we apply our own regulatory oversight to the manufacturing process, and that is going to also require us to develop new methodologies, new SOPs, but also new tools to evaluate the safety and reliability of the manufacturing process.

And so we are looking for institutions that are helping to develop those tools. As I mentioned, there are a number of them, including one in my hometown, but UConn also had a good program in doing this.

Mr. PALLONE. Thank you so much.

Thank you, Mr. Chairman.

Mr. BURGESS [presiding]. The chair thanks the gentleman. The gentleman yields back.

The chair recognizes the gentleman from Michigan, Mr. Upton, the primary sponsor of the Cures bill, 5 minutes for your questions, please.

Mr. UPTON. Well, thank you, Mr. Chairman.

I know that Diana DeGette and I appreciate all the kind words here today, but I just want to remind everyone that it was everyone on this committee as we passed it 51 to nothing. We had wonderful staff who worked plenty of weekends for lots of the year. We had a leadership on both sides of the aisle. We had an administration. And we had the appropriators. So together we did this, and it was a great victory for sure.

And I know a number of us were at the Ken Burns dinner earlier this week, and I am very proud to say that he is working on a documentary on the NIH that he will be unveiling I believe next year through PBS. And I talked with Dr. Collins earlier in the week. I know that they have done some extensive filming already.

I think that it is important for the American public to see, in a nonbiased way, the great work that the NIH has done and is going to do. And, obviously, this legislation is going to find the cures that so many families desperately want.

I would like to start off just by asking Dr. Collins to explore a little bit more of the All of Us Project. To me, this is exciting. I know a little bit about it. I know that the unveiling is scheduled for next spring. I have some concerns about the privacy element of it in terms of what the individuals themselves will experience or some of the protections that might be there.

How can we help? And tell us a little bit more about it and what it is going to be able to do.

Dr. COLLINS. Glad to. And I appreciate your strong support, and that of this entire committee, for the concept that we are trying to pursue here, which is the largest-ever contemplated longitudinal cohort study in the United States of individuals across a wide diversity of ages, ethnicity, socioeconomic status, race, and so on.

And this is going to be a platform for discovery for almost everything you want to know about what allows people to stay healthy, and what happens when illness strikes, and how can we best take care of it.

I appreciate your mention of the Ken Burns film, by the way. And I hope members of this committee had a chance to see, earlier this year, the "First in Human" series that was 6 hours on Discovery Channel about what it is like to be involved in a clinical trial at the NIH Clinical Center and what goes through all those experiences in terms of trying to find answers for untreatable diseases. It was inspiring and emotionally powerful.

The All of Us Program is really a dream for many of us that we have had maybe for a couple of decades but has only become recently practical. We are counting on this million strong group of Americans to be our full partners. As I mentioned in the opening statement, we are doing a beta test right now. We have enrolled about 9,500 individuals just to see how the pieces of this are going to work.

Mr. UPTON. And how long does that beta test take? I mean, for the individual when they come in. Is it a blood sample? What is it that they do?

Dr. COLLINS. It is blood sample. It is a series of fairly simple physical measurements. It is answering a whole series of questions in a questionnaire at your own convenience. And it is, of course, a detailed consent process so that people know what, in fact, they are getting into.

You asked about privacy. And everybody is worried about that. And we are as well. And this is a program that has to maintain the highest standards of privacy and security in order to be credible. And we are working with partners that are top of the market here in terms of doing that. One of our major partners is, in fact, Verily and Google.

And all of the patient identifiers are stripped off before any of the data is actually moved into a location where researchers have access to it, and everything is encrypted end to end. We have already been doing a series of penetration tests and hack-a-thons to see whether there are weak spots in this enterprise. And so far it is looking really good. But we are not going to do the full launch until we are absolutely convinced that all of those parameters have been taken care of.

Mr. UPTON. So when that volunteer participates in the program, how often will you come back to that individual? And what information will they continue to transmit over the rest of their lifetime?

Dr. COLLINS. That is critical, because we do want people to feel like this is something they are proud to be part of it, it is giving them information back. Retention is going to be critical over decades. So they will be getting information back about themselves in terms of blood test results, ultimately their DNA analysis, which

is going to get started sometime next year, as well as giving them information about how they fit in with the rest of this million-strong people. So we will be in touch with them at least every couple of months, seeking constantly to hear from them, what they like, what they don't like. They are really at the table here in designing this with us.

Mr. UPTON. So a lot of us are very familiar with the private group 23andMe.

Dr. COLLINS. Oh, yes.

Mr. UPTON. Where people actually send their saliva. Is this going to be somewhat similar to that? Is it going to be more extensive?

Dr. COLLINS. So 23andMe is a commercial operation which many of us, including myself, have taken advantage of. It does give people genetic information back. We have learned a lot from them in terms of how they do their educational materials to explain things that can be a little complicated in a sensible fashion that people can absorb.

But we are going to give more than that. We are also interested in environmental exposure.

Mr. UPTON. I know my time is rapidly expiring. But I know that your predecessor we worked with at the FDA on 23andMe to make sure that this could actually be launched in a successful way. So I presume that you will be working very closely with the FDA on this to make sure that it meets all the proper requirements.

Dr. COLLINS. So FDA has worked, I think, very effectively in this space, if I can speak for my colleague here, in terms of figuring out how to do the right balance between protecting consumers against fly-by-night genetic tests that are giving you inaccurate information versus those where people are really interested. And I think they have got the balance just right.

Dr. GOTTLIEB. And also trying to develop a framework. We have taken a firm base approach to the regulation of these kinds of consumer genetic testing technologies and announced that about 2 weeks ago, where we are going to allow the test platforms themselves to iterate and regulate the firm itself to make sure it has good SOPs in place and then allow them allow them to go to market with iterations to their test the same way we approach digital health.

Mr. BURGESS. The chair thanks the gentleman. The gentleman yields back.

The chair recognizes the gentlelady from Illinois, Ms. Schakowsky, 5 minutes for questions, please.

Ms. SCHAKOWSKY. Thank you so much. I really appreciate, Dr. Collins and Dr. Gottlieb, for your being here today.

One of the most critical components of the 21st Century Cures Act was providing the NIH with the \$4.8 billion in new funding. And these dollars are certainly critical in advancing research and many meaningful initiatives, like precision medicine and the Cancer Moonshot, as you mentioned, Dr. Collins.

But we must have a serious conversation about drug prices and we need to do more to address this growing problem. If we are spending billions to incentivize the development of new drugs, I think we also have to ensure that patients can afford those drugs.

The development of new drugs and devices is meaningless unless the discoveries are affordable to patients. It is almost cruel to find a cure and then have it priced so high that a patient can't afford it.

I hear from my constituents that the cost of the drugs that they pay for, that they need, is far too high, and that they are frustrated that they are paying twice for their prescription drugs, once in taxpayer dollars, funding for drug discoveries, and then again at the pharmacy.

So, Dr. Collins, here is my question. I know that scientists dedicated their lives, your life, to make discoveries that make the world a better and healthier place. As NIH is funding research that will lead to the development of therapies, do you think that patients should be able to afford the drugs that result from your NIH-funded research and that hard work?

Dr. COLLINS. So this is, obviously, a topic that is on many people's minds. The designate for HHS Secretary yesterday said, yes, we do have a problem with drug pricing. Everybody agrees that this is a serious issue.

NIH has some roles to play but not to the degree that perhaps the public wishes or you might wish that we do. What we can do is to try to be sure that we are doing the front end of drug discovery, which is to identify the right targets and then to develop a pathway towards turning those into therapeutics as efficiently and accurately as possible so that the failure rate for drug development is not so incredibly high as it currently is.

One of the reasons that drugs are so expensive is because the industry has to compensate for all those failures, which are over 95 percent depending on how you count. If we had a success rate of, let's say, 50 percent instead of 5 percent, you can imagine how the equation would look a lot different.

Our goal—and the National Center for Advancing Translational Sciences, NCATS, is a big part of that—is to try to do better in terms of identifying ways to be more efficient, ways that we could do toxicology more cheaply, and other things such as that.

But when it comes to actually having a role in determining the cost, the price of a drug once it has left NIH's hands, it has been commercialized—which it needs to be, we don't make pills—we don't really have any levers to pull in that situation. We depend on other places to do so.

Ms. SCHAKOWSKY. Well, let me ask you this. First of all, you mentioned a kind of calculation, how many failures there are. We do not know that. We have asked for transparency of how much is actually spent to develop. We would like to see that data.

But has the NIH ever exercised what I think is its right under these licenses to ensure that publicly funded drugs are reasonably priced?

Dr. COLLINS. I believe you are referring to the march-in rights, which are a component of the Bayh-Dole Act. We have looked at that and have been asked on a couple of occasions to see whether that would apply in a case where a drug price seems to be unduly high and NIH has played some role in its early development.

But if you look at the language of the bill, it really intends to cover a circumstance where a drug is simply not available to the

public under any circumstances, and then NIH is entitled to step in. This is a little different when it is available but at high cost. Our legal experts don't feel that the law actually puts us in a position to step in.

Ms. SCHAKOWSKY. I thank you for that. I do understand that it is outside NIH's purview to always ensure that the drugs are reasonably priced. But, really, I think we need to be partners in figuring out this piece, because I believe that some of the calculations and some of the prices really do say that many people are not going to be able to access the cures that are available that are shortening their lives. So I appreciate that. Thank you.

Dr. COLLINS. Glad to work with you in any way we can.

Ms. SCHAKOWSKY. I yield back.

Mr. BURGESS. The chair thanks the gentlelady. The gentlelady yields back.

The chair recognizes the gentleman from Illinois, Mr. Shimkus, 5 minutes for questions, please.

Mr. SHIMKUS. Thank you, Mr. Chairman.

Again, welcome. We are glad to have you here. Kind of an exciting day, and it is fun to talk about this. And what I am enjoying about the hearing is hearing my colleagues on both sides address issues that we have both been working on, either separate at some time, then jointly.

So Gene Green and I have picked up Phil Gingrey's work and worked on the ADAPT Act. So my first question kind of deals with—to Commissioner Gottlieb. We know the success we are having. The question is, are there additional policies that we might be able to do to even help in the guise of economic incentives that would help move on this antibiotic resistance attack and being able to get drugs quicker to the market if needed?

Dr. GOTTLIEB. Congressman, I would be happy to work with you on thinking through what additional steps we can take. We do have a platform now and a tail wind of some really extraordinary legislation that has just been passed in recent years. As you know, the GAIN Act did provide additional incentives through exclusivity for the development of antibiotics that were targeted to unmet medical needs. It is the kind of situations you are talking about.

And we are still in the early days of implementing LPAD and the ADAPT Act. We are going to put out guidance, as I mentioned, this summer sketching out the framework for how we intend to implement that.

And we have had multiple pre-IND meetings with sponsors. We think that this is going to grow into a robust tool for trying to get earlier, more expedited approval of drugs targeted to these special situations.

I think there are some things we can do to think about how we reimburse these kinds of products in the marketplace. So to the extent that we are asking sponsors to develop antibiotics that are going to be used on an emergency basis, or a very limited basis, a reimbursement model where you pay per use might not be the most efficient way to provide an appropriate incentive.

So we might want to think of things like site licenses. These are things that have been considered in the past, where hospitals might pay a licensing fee for access to a drug of that nature. That

might provide more of an incentive. That is obviously outside of my scope.

Mr. SHIMKUS. Well, let me jump in here, because one hurdle we haven't overcome, we were told earlier in the process that I have been involved with, was the issue of tradable vouchers, which I didn't get across the finish line.

So my colleagues understand that there is a need, and that may not be the venue. So I would hope we would keep thinking if there is something else that we can do that might get us to the table where we can send another signal about this. And you don't have to talk about it now. Just this is the place to raise that issue.

Let me go on the same line of questioning on antibiotic resistance and talk about just where we are on therapid diagnostic test to be able to identify quicker so that we can intervene earlier. Any comments on that?

Dr. GOTTLIEB. Well, this technology is becoming more and more available at the point of care. We used to rely on blood cultures that would take days to grow out organisms and we would just give sort of broad spectrum antibiotics until we figured out what patients were infected with and we could tailor therapy.

Now you have the ability to sequence organisms or you gain the ability to sequence them at the point of care. We are doing things with respect to next-generation sequencing, in collaboration with NIH, that I think is going to be very important to making these opportunities available.

Dr. COLLINS. If I may, we are running a prize competition right now. And, again, 21st Century Cures had a specific call-out to us to do prizes using the EUREKA part of the bill.

For AMR, we are basically asking competitors to come up with a means within 4 hours of being able to determine what is the infection and does it have multiple drug resistance in the case of a urinary tract infection or pneumonia or sepsis. That would be a dramatic game-changer if we had that information in that period of time. There are a lot of competitors out there. There is 20 million bucks out there for the one who wins this, 10 from NIH, 10 from BARDA. And I think that could be a pretty exciting moment if we can get the technology to that point.

Mr. SHIMKUS. Well, yes. Thank you very much. And I am going to end on this, which is still a positive note.

So I am also very excited about the All of Us campaign. The University of Illinois is involved with it, and that is kind of part of my area. And so it is exciting.

And same issues. We had a telecommunications subcommittee hearing yesterday on big data, algorithms, all this stuff. Then I segued into my visit with Washington University, which is close to my home. I am in the St. Louis metropolitan area. So I know that university well, and I know the associated hospital that they work in conjunction with.

They have been so excited about the passage of the 21st Century Cures Act because in their research—and I toured them just last week during the break and did Alzheimer's, new technologies that really drill down to the cellular structure, antibiotics, which is one of the worlds on which I focus individually.

And they just reiterated the importance of consistency. Sometimes we have been inconsistent in the funding streams, and the 21st Century Cures has established a consistent streaming and commitment to what we are doing in the health-related field. So I want to thank you, and thank you on behalf of the University of Illinois and Washington University.

Dr. COLLINS. If I may, in one sentence, just say thank you all for what you did in the Innovation Fund for 21st Century Cures, providing consistent support over a course of 10 years for these projects, which clearly are going to need that kind of sustained funding in order to be successful. And it is often difficult to see a path for sustained funding in the year-by-year appropriations. So thank you.

Mr. SHIMKUS. I am done. I yield back.

Mr. BURGESS. The chair thanks the gentleman. The gentleman yields back.

The chair recognizes the gentlelady from California, Ms. Matsui, 5 minutes for questions, please.

Ms. MATSUI. Thank you, Mr. Chairman, for holding this hearing today and for Dr. Gottlieb and Dr. Collins to be here today as we talk about the implementation of the 21st Century Cures Act.

As we worked together on this bill, patients were always at the center of our conversations. And as we move forward, patients are still at the center as we implement this bill.

I am particularly concerned with research and drug development that affects patients with rare diseases, because for a small population of patients it is often very hard to get drugs and treatments through the approval process. I just can't tell you how many individuals have come to me with their concerns, in wheelchairs, and with their stories.

Because finding cures for rare diseases is not only important to the patients with rare diseases and their families, but to all of us, because you never know where a cure is going to come from, and often research and drug development on one disease may create results for another. So we need to leverage all the tools that we have.

I would like to hear about some updates, some provisions that I worked on in Cures that were aimed at encouraging innovation for patients with rare diseases. Sections 3012 and 3016 of the law were designed to encourage the development of targeted drugs for rare diseases, including allowing manufacturers to leverage data from previously approved applications for new indications.

We see that all of the time with rare diseases as many patients use drugs off label as their only options, drugs that were approved as safe and effective but not for their specific condition.

Dr. Gottlieb, can you provide an update on implementation of these provisions?

Dr. GOTTLIEB. If I may, Congresswoman, I just want to build on what you said. And I appreciate your comments and your commitment to these efforts.

To the extent there are challenges associated with the development of drugs for rare diseases, sometimes it is difficult to enroll these trials as well. We have taken steps to try to facilitate that.

I think also what we are seeing are situations where, because the biological basis is so well established for some of these drugs and

we can select which patients will likely derive a clinical benefit, we are seeing clinical benefit very early in the development process.

And that was the point of trying to see how we can apply the accelerated approval mechanism to achieve what you outlined, the ability to expedite these products to the market when we do observe an extraordinary clinical response in an early stage trial, knowing we are going to be able to get the confirmatory evidence.

Building on those two provisions that you mentioned, we are going to be releasing very soon a guidance that I first announced probably 3 or 4 months ago that we were developing, which is a targeted therapies guidance. It is going to outline very specifically how sponsors can get approval for products that are targeted to biological markers rather than certain disease tissue states, if you will. So tissue-agnostic drugs.

And the best example would be a cancer that might appear in multiple organ systems but be driven by the same biological marker. If you can demonstrate that a drug targets the underlying biological mechanism, you can get approval now across all those different indications.

We are also, to the point you made, making robust use, in my opinion, especially in the oncology setting, of the provision that allows us to give supplemental indications more easily based on existing data in the public domain or references to literature rather than having to, in many cases, replicate the new clinical trials in those indications where we have a very strong biological rationale to know that the drug works there.

That was the other point of my opening testimony today, the ability to extend approvals in other settings that are proportionate to where the original approval was given. So you approve a drug in a second-line oncology situation, and then making it easier to then extend it into a frontline indication when the evidence starts to accrue.

Ms. MATSUI. Well, thank you very much for that update.

Dr. Collins, how can NIH's Precision Medicine Initiative benefit rare disease patients?

Dr. COLLINS. Precision medicine, as a concept, is trying to get away from one-size-fits-all to identifying the individual characteristics that are going to lead to better prevention and treatment.

While the Precision Medicine Initiative flagship, called All of Us, is not particularly well designed to deal with rare diseases, because even with a million people there may be relatively few with a truly rare disease, the whole rare disease field is very attached to the precision medicine idea.

You can see what has happened with cystic fibrosis, which was mentioned earlier, where we now have therapeutics that are specific for the particular kind of misspelling that that individual has in the cystic fibrosis gene. That is a good example. And we want to see much more of that, because there are at least 7,000 of these rare diseases for which we know the genetic mutation but we don't yet have a treatment.

We at NIH are working hard with our colleagues at FDA on something called the Therapeutics for Rare and Neglected Diseases Program, TREND, which is part of the National Center for Advancing Translational Sciences, because there are some of these dis-

orders that are so rare that industry is not interested, at least initially, in investing in them, although there is more interest now than there used to be in industry.

And I think we are making real headway. And something that the 21st Century Cures bill did was to give TREND the ability to run phase three trials on those disorders which we did not have at NCATS before, and we are grateful for that.

Ms. MATSUI. OK. Well, thank you very much. And I yield back.

Mr. BURGESS. The chair thanks the gentlelady. The gentlelady yields back.

The chair recognizes the gentleman from New Jersey, Mr. Lance, 5 minutes for questions, please.

Mr. LANCE. Thank you, Mr. Chairman.

And good morning to you both.

Dr. Gottlieb from Middlesex County. Is that right.

Dr. GOTTLIEB. That is right.

Mr. LANCE. Very good.

Dr. Gottlieb, throughout the 21st Century Cures dialogue we heard about a number of innovative treatments that companies were pursuing that would target specific genetic mutations in patients with rare diseases. I am the Republican chair of the Rare Disease Caucus here in the House.

This is, of course, quite encouraging. But we have also heard that there can be multiple genetic subtypes of each rare disease and that can further complicate drug development in clinical testing in already challenging circumstances.

To ensure that as many patients can benefit from these new technologies as possible and as quickly as possible, as you know, section 3012 authorizes the FDA to rely on data that accompany previously submitted drugs that use the same or similar technology.

Could you elaborate a little further—and I know you have been discussing this—about the ways in which the FDA has utilized its authority to date and what we should be doing more, perhaps, here at the congressional level?

Dr. GOTTLIEB. Thank you, Congressman. And the provision, I think, that you have built into 21st Century Cures that you are referencing, I think, really anticipated the future and what we are seeing.

The truth of the matter is, it is still early days in terms of the drugs that we are seeing that are targeting in many cases what are inherited disorders where you have a genetic change that drives a disorder but you have multiple subtypes that all produce the same clinical circumstance. And the question becomes, if you study one genetic subtype, when and how do you extend the approval into the genetic other subtypes without requiring the sponsor to enroll in a clinical trial in each one, especially when each one might be only a handful of patients?

We are currently having discussions with sponsors around this very principle. I think what Congress built into the law is giving us the latitude that we need to be thoughtful about how we can think about this and extend approvals across the range of subtypes that drive a common phenotype. And I think you will see us exercising that authority in some upcoming approvals. And we also

plan to address this, to some extent, in the targeted therapies guidance that we will be releasing soon.

Mr. LANCE. Thank you, Doctor.

And how does FDA's familiarity with an underlying technology affect subsequent product applications and the supporting data the agency expects to be included?

Dr. GOTTLIEB. Well, I think our ability to understand how the product works and how it intervenes in the molecular basis for a disease is what drives our ability to make these extensions that you are talking about and give us confidence that a drug that works in one setting is going to have the same clinical performance in another setting where there might be a slight genetic variation but it leads to the same phenotype. So what you reference is instrumental in our ability to make these determinations.

Mr. LANCE. Thank you.

I was pleased that language was included in the bill authorizing grant funding for the study and expansion of continuous manufacturing. New Jersey has been a leader in this area, including our state university, Rutgers, and others as well, bringing together research institutions and industry to advance technology.

What steps are being taken by the FDA to carry out the language included in the act regarding what I have just discussed?

Dr. GOTTLIEB. This has been a very high priority for the agency trying to facilitate the development of a platform for continuous manufacturing. We are going to continue to give grants to institutions that are helping to develop the tools that are going to enable us to continue to move this forward.

We think continuous manufacturing represents the future. It is going to provide a much, much more robust way to manufacture products, especially some of the newer products that we are seeing. We think that it provides certain safeguards from potential drug shortages.

And I think it also might help us repatriate manufacturing back here to the United States. The ability to manufacture off a small footprint that is driven by high technology lends itself to domesticating that process as opposed to outsourcing it to other countries as we have seen with traditional manufacturing. So I am hopeful that this is also going to help us build up a robust domestic industry.

Mr. LANCE. Thank you. I certainly encourage repatriation. And congratulations on your appointment and your confirmation. And, Dr. Collins, it is always a pleasure to be with you, and I look forward to being with you again at NIH, particularly on Rare Disease Day.

And, Mr. Chairman, I yield back 8 seconds.

Mr. BURGESS. The chair thanks the gentleman.

The chair recognizes the gentlelady from Florida, Ms. Castor, 5 minutes for questions.

Ms. CASTOR. Thank you, Mr. Chairman.

Dr. Collins, the 21st Century Cures Act funded NIH to provide support for biomedical research through the NIH Innovation Fund. This focused on four vital research priorities to address some of the greatest challenges in disease prevention and treatment.

Back home in Tampa, we are home to the only NCI-designated cancer center in Florida, the Moffitt Cancer Center. And just in my short time in Congress I have been floored at the progress that we have made in treatments and cures for cancer. And yet, there is so much more to be done. And I think the Beau Biden Cancer Moonshot that is part of 21st Century Cures is an exciting research initiative because it will accelerate cancer research and improve screenings and treatments for cancer.

Can you discuss some of the research that the Beau Biden Cancer Moonshot Initiative is funding and how it may contribute to addressing the burden of cancer across the country?

Dr. COLLINS. Yes, I would be happy to.

We convened a blue ribbon panel of some 28 individuals who are the most visionary folks we could identify to figure out what would be the best way to take additional resources coming forward from 21st Century Cures and do things that we otherwise wouldn't have been able to do. And they came up with a series of 10 different areas that were ripe for further investment.

And I don't have time to go through all of them. I will just mention one because it is so much on everybody's mind right now as a source of great excitement, and that is the area of cancer immunotherapy.

This, which for 40 years has been labored by a very small group of people, particularly Dr. Steven Rosenberg at the NCI, has arrived in the last few years as the most exciting development in cancer treatment in a very long time. We have had surgery, we have had chemotherapy, we have had radiation, and that was sort of it.

And now we have a fourth modality, and a modality which, when it works, is capable of taking somebody with widely metastatic disease from melanoma, or somebody with advanced leukemia or lymphoma, and not just providing a response, providing what appears to be a cure. And when you see that, it is enough to make you believe that we should put every bit of energy in this to figure out how to get it to work for all cancers.

And that is what the Moonshot is making it possible for us to do. Working with industry and this partnership that we just announced a month ago, we are trying to figure out why doesn't it work when it doesn't and what could we learn from that. Why doesn't it work for pancreatic cancer? Why doesn't it work for most cases of prostate cancer or breast cancer? It seems to work for a certain subset, but the immune system ought to be able to recognize those cancers too. What can we do to find that answer, working closely with our colleagues at FDA in this?

And you have probably heard that just in the last few months the first so-called CAR-T cell approaches to leukemia and lymphoma are being approved, which is an example of this.

So, again, thank you to the whole Congress for recognizing that this was one of those areas that was ready for a big boost. And the \$300 million—

Ms. CASTOR. Well, I share your excitement for immunotherapy. I have heard it directly from my researchers at home and from families now, that they have additional hope in their life.

How about Alzheimer's disease? Give us the same sketch for hope and promise now under the 21st Century Cures Innovation Fund in Alzheimer's.

Dr. COLLINS. So 21st Century Cures funded the BRAIN Initiative, which is an incredibly ambitious effort to understand how those 86 billion neurons between your ears do what they do, and each one of them with maybe a thousand connections. And that is going to provide us with this foundation of information about neuroscience that we just have not had.

There is a huge effort, of course, more directed at Alzheimer's disease, and Congress has been increasing our funding through the regular process.

Ms. CASTOR. Right. There hasn't been enough in the past.

Dr. COLLINS. And it has been going up wonderfully well. And we are now in a position, I think, to take both the basic science coming from the BRAIN Initiative and the clinical applications that are possible through the regular appropriation and really turbo charge this effort to come up with answers.

And we need those answers, as all of us know who look at those 5 million people who are already affected and look at what is going to happen in the next few decades with the aging of our population if we don't come up with a solution.

I am guardedly optimistic, although this is a really hard problem, that we are on the path that is going to figure out what to do to prevent this disease in those who are at high risk before it even strikes.

Ms. CASTOR. How can the public monitor progress here? You might go online and do a Google search, but that won't get to the heart of the matter of what is happening over the coming years because of these investments.

Dr. COLLINS. So we try our best through NIH to make public information available, but we don't think it is appropriate for us to be out there marketing what we do. So we are educators, but we are not necessarily doing the best job of communicating to people who are interested. We count on the media or we count on interested advocates to get the word out, particularly the Alzheimer's Association and other advocates like that.

And I do think the consciousness of the public has been raised about this. But in terms of tracking what is happening month by month, we need better opportunities to do that. I agree with you.

Ms. CASTOR. Thank you very much. I yield back.

Mr. BURGESS. The chair thanks the gentlelady. The gentlelady yields back.

The chair recognizes the gentleman from Florida, Mr. Bilirakis, 5 minutes for questions, please.

Mr. BILIRAKIS. Thank you, Mr. Chairman. I appreciate it.

Thank you for your testimony.

Dr. Collins, as one of the co-chairs of the Congressional Parkinson's Caucus, I was proud that we included a neurological condition surveillance system as part of Cures. It is estimated that one in six people suffer from neurological disorders. This neurological surveillance system would gather information about patients, including incidences, prevalence, and also demographics and outcome measures.

I know that the CDC would run the surveillance program, but NIH has the experts that would use the data. How will having this information available to NIH assist biomedical research at the agency and in the research community at large?

Dr. COLLINS. Thank you for the question.

That feature of 21st Century Cures, which as you point out is assigned to CDC to develop this neuroscience assessment of prevalence and incidence of neurological conditions, it is certainly something that if the data were available we would find it quite useful. I think at the present time, because of the funding issues, CDC has not been able to act upon that.

We are certainly deeply invested in Parkinson's disease research, including working with industry on something called the Accelerating Medicines Partnership. It is possible that the All of Us program that is going to enroll a million Americans over the course of the next 3 or 4 years will provide some useful information here because some of those folks are going to have Parkinson's, quite a few, in fact, when you consider how frequent the illness is and the fact we are talking about a million people.

But it won't quite substitute for what you asked CDC to do. I think this is a circumstance where the ability to get the information is not trivial. It takes a lot of resources, a lot of time. And here is where CDC, as I understand it, is having a hard time figuring out how to actually do what Cures Act asked them to do.

Mr. BILIRAKIS. Thank you.

Dr. Gottlieb, during my Cures roundtables in my district I heard from a woman who had a child with Duchenne Muscular Dystrophy. She talked about two hurdles: the challenge of acceptable biomarkers and the need to incorporate patient-reported data. In Cures, we had a provision dealing with patient-reported data, as you know.

You mentioned in your testimony there is a new section on patient experience data. Can you update us on when that came online, how FDA will incorporate that data in the review process, and what does FDA hope this type of feedback will lead to?

Dr. GOTTLIEB. We are starting to do that right now, Congressman. Cures did give us the ability to expand on these opportunities to try to build in better measures of the patient experience as a measure of how we look at efficacy for purposes of approval.

I think the opportunities that we are going to have that I am most excited about are better opportunities to look at things like physical performance. So you talked about Duchenne Muscular Dystrophy. One of the objective endpoints that we use in measuring outcomes in that clinical setting is traditionally a walk test that is meant to approximate physical function and look at whether or not new therapies are improving physical function or slowing the rate of decline in that clinical setting.

But what if we had a tool that allowed a patient to wear a device, maybe it is a watch, that measures their physical performance in routine daily living? That might be very preferable to trying to do it in an artificial setting of a clinical trial where you are doing it in a sort of random fashion when a patient comes into a doctor's office for an evaluation or checkup. If you are able to look at a pa-

tient in their daily life, that might provide a much more objective measure of how a drug might be impacting their life.

And so these are the kinds of opportunities that I think we have with new technology. They are the kinds of opportunities that I think that this legislation is giving us the legal basis to make better use of. And this is what I am looking to the future for.

Mr. BILIRAKIS. Very good. Thank you.

Again, Dr. Gottlieb, the other issue that was brought up in my roundtable was the challenge of acceptable biomarkers. This has been an issue that I have brought up in prior hearings.

Can you update us on changes FDA has made? And how can we encourage the greater use of biomarkers, particularly for rare disease patients where traditional clinical trials may be too hard for them to—they are limited in population, as you know. So if you could answer that, I would appreciate it.

Dr. GOTTLIEB. Thank you, Congressman.

Here, again, Cure has provided us with new opportunities. The legislation did provide us an opportunity for the incorporation of drug development tools into our regulatory process. We have a biomarker qualification program now. We have eight biomarkers that are under consideration, all by various consortia.

We also have another program that allows us to develop other kinds of measures that can measure efficacy or performance of patients in clinical settings. And we are going to qualify the first, for major depressive disorder, very soon, a new survey tool that looks at outcomes for patients who are suffering from MDD in the clinical setting. Again, this was a qualification process that was created by Cures as well.

So these are moving forward. We are seeing a lot of interest in these kinds of opportunities, and we think this is going to provide a very important framework for the future.

Mr. BILIRAKIS. Excellent. Thank you very much.

I yield back, Mr. Chairman.

Mr. BURGESS. The chair thanks the gentleman. The gentleman yields back.

The chair recognizes the gentlelady from Colorado, 5 minutes for questions, please.

Ms. DEGETTE. Thank you, very much, Mr. Chairman.

One of the proudest achievements we had in 21st Century Cures, I thought, was the establishment of the Oncology Center of Excellence at the FDA.

Dr. Gottlieb, as you mentioned in your testimony, this first-of-a-kind center enhances coordination between the FDA's drug device and biologic centers to leverage the agency's expertise on cancer. I am hoping that the OCE model will be a success that we can use for other diseases. Can you tell us what this center is already doing to advance the work in cancer treatment?

Dr. GOTTLIEB. So we have already been able to use the center to do consolidated clinical assessments on a range of products. I think the most profound sort of manifestation of the opportunity that such a center affords us is what we saw with respect to the approval of two gene therapy products targeted to some rarer cancers that I think do provide a meaningful opportunity, and perhaps a profound opportunity, for patients to get more advanced and poten-

tially more curative therapy in settings where there wasn't very good available therapy prior to the approval of these products.

I think the essential point is that the center allows us to consolidate the clinical review and take a more multidisciplinary approach to how we look at the evaluation of efficacy and safety around these products. And we do think that this kind of center approach represents the future of how we want to approach other therapeutic spaces.

Ms. DEGETTE. For other diseases?

Dr. GOTTLIEB. Immunology, a center for neuroscience. These are things we are contemplating. Now, it is very important that we get it right in the setting of oncology since this is our test case and our first model for this.

Ms. DEGETTE. And can you do more if you get full funding for this center?

Dr. GOTTLIEB. Well, we appreciate what Congress tried to do in appropriating funds to the center through NIH. As Dr. Collins will attest, there have been some challenges associated with transferring those funds to FDA, some legal challenges.

And so we look forward to continuing to have discussions about how we could fund this. It hasn't been funded to date in part because of the challenges associated with how the money was allocated, to nobody's fault. So we do want to work on that.

Ms. DEGETTE. It is a frustration for us too. So if there is something we can do to help, let us know.

I just have a couple of more quick questions. I want to ask about the IRB provisions. You guys know that for about 10 years I worked on a Protection for Patients in Research Act that would streamline the IRB process, and I was really happy to get some of that signed into law as part of Cures.

I know that many of the IRB provisions in Cures have not been implemented yet, but I am hoping maybe you can talk to us about how the Cures provisions that streamline the IRB process will help reduce administrative barriers for scientific research.

And we will start with you, Dr. Collins.

Dr. COLLINS. Quickly, I think it has been very helpful to have those features in the Cures Act. One thing that we are now insisting upon is that multisite trials, which used to have multiple different IRBs, each of which might have some opinions about the wording of the consent form, we no longer think that that is the right way to do things. And having a single IRB for multisite trials has now become the norm. And, basically, if that is not to be the case, we need to understand why.

And your support for that has been really helpful because we generally lost many months in the process of trying to—

Ms. DEGETTE. We lost many months, and we lost many millions of dollars every time we did a research study.

Dr. COLLINS. Indeed. So this makes a lot of sense, and we appreciate the opportunities to do that.

Ms. DEGETTE. And sort of a related issue, and that is the clinical trials. The Cures provisions establish processes at the FDA to qualify biomarkers, incorporate patient experience and real-world evidence into trials. The committee recently built on the Cures provi-

sion in the FDA Reauthorization Act. What more can we do to improve the way and modernize the way we are doing clinical trials?

We can start with you, Dr. Gottlieb, on that one.

Dr. GOTTLIEB. I think that there is a lot we can do. And here again, Cures gives us a platform for doing it. And this is one place where I think that we are trying to take the spirit of what Congress did in Cures and wanted us to do and extend it.

And so we are looking at opportunities to build in more modern approaches to how we design clinical trials, more adaptive designs, seamless clinical trials, other ways to make clinical trials easier to enroll and allow us to get measures of clinical benefit earlier. There is a lot we can do, I think, to think differently about how we move away from a very old paradigm for design of clinical trials and modernize these approaches.

Ms. DEGETTE. So I will just ask both of you for all of these issues I am talking about. If you need additional legislative authority, please let us know so that we can work together in a bipartisan way to expand this. Because I think this is really going to help us get cures much more quickly to approval.

And thank you, Mr. Chairman. I yield back.

Mr. BURGESS. The chair thanks the gentlelady. The gentlelady yields back.

I am going to recognize myself 5 minutes for questions. I delayed at the beginning.

Let me just pick up on that point that Ms. DeGette just made. This is, of course, our first oversight hearing on the Cures bill and it is the 1-year anniversary of the House passage of the legislation, but really the lines of communication should be constantly open.

And I would just echo what she said. If there are statutory changes that need to be made to give you the flexibility to deliver the products we want you to deliver, we would like to hear from that. Let's not wait another year to have those discussions, is all I would say.

Both of you—and I have got several questions that I will probably submit for the record because I am going to run out of time—but each of you mentioned a specific disease that I would like just a little bit more information.

Dr. COLLINS, you mentioned sepsis.

And, Dr. Gottlieb, you mentioned sickle cell.

On the issue of sepsis, you said a 4-hour diagnostic. My generation of physicians, you had to draw blood cultures so many hours apart. Two weeks later, if they grew something, great, then you isolated the bacteria. You put it on Kirby-Bauer sensitivity media. Seventy-two hours later, you would have the antibiotic to use if the patient was still with you. And you talk about a 4-hour timeframe. That is pretty incredible.

Dr. COLLINS. It is. And it is still not a reality, but I can tell you the competitors for this prize are coming along pretty quickly. We already narrowed it down to a manageable group that is making notable progress.

Yes, I am in the same generation of physicians you are, Dr. Burgess, and the idea of waiting all that time. Because, of course, what did we do then? We basically had to give every imaginable possibility, cover it, with the appropriate antibiotics, which meant every-

body got broad spectrum antibiotics, probably got steroids, probably got all kinds of other support without really knowing what we were doing. We were flying blind.

We want to take the blinders off and get the technology that is now capable of doing this. And much of it is based on genomics, the ability to find the DNA of that organism and have it tell you what that organism is capable of. There is no reason we can't do that.

And yet, you are right, it took a long time to get to the point of actually talking about this as a reality. Even a few years ago most cases of sepsis were being managed pretty much like you and I did when we were residents.

Mr. BURGESS. Empirically, never use one drug if three will do. Yes, I remember those days.

Dr. Gottlieb, you mentioned sickle cell. And it wasn't really part of the Cures bill, but at one of our reauthorization hearings in this room probably a year and a half ago the statement was made it had been 40 years since the FDA had approved a new sickle cell drug.

And you talk that there is one now that is on the horizon or has it been approved? Could you elaborate on that?

Dr. GOTTLIEB. This is a reference, Congressman, to gene therapy. We are seeing products in development using tools of gene therapy targeting a range of blood disorders, including sickle cell disease.

Gene therapy lends itself—I think some of the early applications of it that we are going to see are going to be what we call ex vivo applications where you take cells out of the body, you manipulate them with genes, and you reinsert them in the body.

And one of the opportunities is around the ability to do that to blood cells. And we know that if you can get patients with sickle cell disease to express more fetal hemoglobin, you can treat the underlying disease. You don't cure it, but you effectively dramatically reduce the phenotype.

And so there are approaches like that, trying to use gene therapy to change the nature of blood cells in these patients where you take them out, you change them to express fetal hemoglobin, and then you put them back in.

I will just close by saying these aren't going to be risk free. So it is going to be important that we carefully select the patients who are going to benefit the most from these kinds of approaches. But we are going to see these opportunities, I believe in the near future, if not in sickle cell disease, in other blood disorders.

Mr. BURGESS. And, again, my point, for illustration, was the very long time horizon between the FDA's approval of the last sickle cell medication. And it is encouraging there is something on the horizon on gene therapy.

And I heard a discussion from a couple of researchers yesterday about some retinal diseases that they were targeting. And, again, this just seems like something that is tailor made for surrogate endpoints to be able to use either the perception of light, the restoration of vision, able to read a certain size print.

And it was a one-time therapy, which then gets into the whole issue, how do you price something that is only given one time? If

it gives you back your sight, it is probably worth a lot as far as value to the patient.

I am sorry, Dr. Collins, you wanted to say something?

Dr. COLLINS. I was just going to say with regard to sickle cell, there is a protocol now in the clinical center at NIH that has treated more than a dozen patients using a gene therapy vector, and it gets better and better as they keep refining it. And there are individuals now in that protocol who have essentially normal hemoglobin values and who say they have never felt better, they are free of those horrible crises that were part of their life.

We are really making progress in this space. But it has got a ways to go to be sure that the risk—because you have to do something to make space for the corrected cells in the bone marrow. So you have to do a limited ablation. That is not a trivial thing to do, and we need to be sure we are getting that part right.

Mr. BURGESS. Well, I appreciate the update. That is encouraging.

And I would just say, several years ago, I guess it has been over a decade ago, I had the opportunity to talk to Dr. DeBakey. We gave him a gold medal honoring him here in the House of Representatives.

And one of our discussions, he and I went down to the VA the next day, and he told me when he graduated from medical school—and I guess it was sometime in the 1930s—he said: “I knew I wanted to go into research, I knew I wanted to be a researcher, but there was nowhere in America to go, and I had to go to Germany in order to learn how to be a researcher, to get the credential to be a researcher.”

Now scientists come from all over the world to the National Institutes of Health to get the credential to be a researcher. I hope Ken Burns reflects that in his opus.

Thank you. I will yield back my time.

And who am I recognizing next?

I recognize Mr. Cárdenas from California, 5 minutes for questions, please.

Mr. CÁRDENAS. Thank you very much, Mr. Chairman, and also Ranking Member Green. Thank you so much for having this really important hearing.

Implementing 21st Century Cures, so far it appears we are doing a pretty good job of making progress. And so I want to thank you for that. And also if you could please share with your team our thanks for doing all that good work with the law that we passed here. Also, I want to thank you two gentlemen, doctors, for your service.

My first question is—we will start with FDA—are there any vacancies in your department?

Dr. GOTTLIEB. There are, Congressman. We are undertaking a process to try to reform our hiring system. I think, as you know, we have had challenges onboarding people in a timely fashion, and that has led to a backlog of vacancies that we are very focused on addressing.

Mr. CÁRDENAS. Do vacancies in any way contribute to a slowing down of the incredibly important work and progress of saving lives?

Dr. GOTTLIEB. Yes. The truth of the matter is, you can always do more with more. It is hard for me to argue that if we are down

hundreds of slots in our drug center, for example—and I think that is what you refer to—that that doesn't have an impact on the overall operation.

We recently launched a hiring pilot around the user fee slots, and we are going to announce very soon the results of the new hiring process that we are going to be implementing on a pilot basis that dramatically shortens the time that it will take us, we believe, to onboard a new hire. If that pilot is successful, we plan to try to roll it out on a wider basis across the agency.

Mr. CÁRDENAS. Thank you.

And same question to NIH. Are there any vacancies in your department?

Dr. COLLINS. So we are fortunate in that more than 80 percent of the dollars that go to NIH go out in grants to institutions all over the country, in all 50 states. And so the work that we support largely doesn't get done within our own four walls. We do have an intramural program which is about 11 percent.

Mr. CÁRDENAS. Do you have vacancies?

Dr. COLLINS. We do in that area because we are always turning over. And there was a hiring freeze at the beginning of the administration, which we are happy to say we have now come to a place where we are able, for the most critical hires, to be able to bring people on board.

Mr. CÁRDENAS. So there is a semi-freeze still? Critical hires, you make the point, you get to hire them, but others are still in abeyance?

Dr. COLLINS. We are very focused right now on ways that we might be able to improve our administrative efficiencies. So Dr. Tabak, who is my principal deputy, and I are looking at all the hires very carefully and personally to be sure that we are making the right—

Mr. CÁRDENAS. And as well you should. I am not questioning your practices. My real question to you on that front is, what can Congress do to help you be more efficient of filling those vacancies, if there is anything that we can help in that, effecting a better, streamlined process?

Dr. GOTTLIEB. Cures is going to help with the resources that you provided to us to be able to go out and target hires with certain technical expertise where we have a hard time competing on a salary basis with people with extraordinary expertise. And so that is helpful to us.

I think that our challenge—we don't have a hiring freeze in place right now, we are able to move on hires—our bigger challenge has been the length of time it takes to onboard someone and the fact that if you are recruiting a medical reviewer who is a physician in an academic institution looking to make a career move and it takes us 12 months to bring them on, they might take another job in that interim.

And so we need to find processes that allow us to compress that timeframe. We think we have done it. I have pulled over from Cedar one of their very senior executives, an extraordinary woman who is a very senior manager, worked at NIH for a while, to head up this hiring pilot. And we are very focused on trying to make this work with respect to the PDUFA slots. And then, if we can validate

our new hiring template that we will be rolling out soon to provide transparency around it, we will implement it on a wider basis.

Mr. CÁRDENAS. Thank you.

In the interest of time, I want to get to my last question. And if you could please think of Max asking you this question and try to keep your answer short. I only have 30 seconds left.

If Max were to ask you, "Should we continue to help people become scientists and doctors and get an education?" should we continue to help them do that?

Dr. COLLINS. Not only should, we have to. That is the future.

Mr. CÁRDENAS. OK. So if Congress actually took away some of the little things that help them get their education, would that be a good thing or a bad thing?

Dr. COLLINS. That would not achieve the goal that we all would have to agree is critical for our future.

Mr. CÁRDENAS. Remember, you are talking to Max. Is that a good thing or a bad thing?

Dr. COLLINS. It is a bad thing, Max.

Mr. CÁRDENAS. Thank you. Thank you very much.

I yield back the balance of my time.

Mr. GUTHRIE [presiding]. The gentleman yields back.

And the gentleman from Indiana, Mr. Bucshon, is recognized for a 5 minutes for questions.

Mr. BUCSHON. Thank you, Mr. Chairman.

Commissioner Gottlieb, as physicians we share a common desire to ensure patients see tangible benefits from advancements in science and medicine. The 21st Century Cures Act law laid a critical foundation to advance personalized medicine, especially as it relates to therapeutics.

One area which was not really addressed by Cures was improving the regulatory paradigm for clinical diagnostic tests, which are often the entryway into personalized medicine. Both FDA-approved in vitro diagnostics and laboratory-developed tests have experienced incredible growth in terms of the number of tests offered in the market and the levels of their complexity. So physicians and patients rely on these tests more and more to make critical, life-altering decisions.

Unfortunately, the diagnostics regulatory framework remains outdated, inconsistent, and insufficient, leading to potential patient safety concerns and barriers to innovation, in my view. Congress needs to do more, and I applaud your recent statements that it is time for legislation in this area.

My colleague and I, Diana DeGette, released a discussion draft of the Diagnostics Accuracy and Innovation Act, DAIA, as you probably know, which aims to modernize the regulatory framework for diagnostic tests. Notably, the DAIA would create a new pathway to regulate clinical diagnostic tests outside of the medical device framework while ensuring consistent regulation regardless of the test developer.

We believe the DAIA takes the best of what the FDA, CMS, and the states have to offer and creates a new, modernized regulatory paradigm building on the expertise and capacity of these critical entities.

I am pleased that the agency, the FDA, is working now on technical assistance on the draft legislation, and I look forward to working with you and the agency to make the diagnostics reform a reality of this Congress.

So the question I have is, what is your sense of what improvements need to occur in this important area and how it relates potentially to the personalized medicine space and how Congress can be helpful?

Dr. GOTTLIEB. Thank you for the question, Congressman.

As you know, we for a very long period of time exercised enforcement discretion with respect to this entire space. But I think as we see these technologies become more sophisticated and become more important to the clinical practice of medicine, and as we see some variability in the quality of the products that patients are using, on which they are making very important medical decisions, we do think there is a role for FDA to play in certain aspects of these products and across certain products.

But we also believe that the traditional medical device approval process is a poor fit for the regulation of LDTs, laboratory-developed tests. And we think that there is an opportunity, in our view, to fashion a regulatory framework through legislation that can provide a more appropriate fit to the kind of technology we are talking about here.

And so we are very eager to work with Congress on this. I think the opportunity couldn't be more ripe to do that. I think that the clinical opportunities for patients couldn't be more seductive and the need to do that.

So we will provide whatever support and technical assistance we can to Congress, including the white paper that we put out, which laid out some of our thinking on this.

Mr. BUCSHON. Thank you very much. I appreciate that.

Ms. DEGETTE. Will the gentleman yield?

Mr. BUCSHON. Yes. I will yield to Diana DeGette.

Ms. DEGETTE. Thank you.

So, Dr. Gottlieb, we really want to get going on this early in the new year. So the quicker we can get that technical assistance, the better.

Thanks.

Mr. BUCSHON. Thank you.

This is just kind of a doctor thing. I was a doctor before. So, Dr. Collins, I am interested in, the NIH many years ago, as you know, interleukin treatment, which is an immunotherapy type treatment, maybe 25 years ago even, especially as it relates to malignant melanoma I think—

Dr. COLLINS. Exactly.

Mr. BUCSHON [continuing]. The NIH pioneered a lot of that work. Now it is 20 years, 25 years later, or whenever the date is, but I remember this from my residency in medical school.

I mean, we are in an exciting time, but it has been quite a long time since immunotherapy has really been something we have been trying to develop, right? What do you think has slowed us down? I know we have gotten to a good place now, but what do you see as the barrier to actually getting us across the finish line to making this better?

Dr. COLLINS. Well, Dr. Bucshon, it is a good example of how you have to build over many years from basic science efforts, from a lot of failed hypotheses, ultimately building the strength to understand how the immune system can be brought to bear on cancer. And now, understanding things like checkpoint inhibitors and how you can take immune cells out of the body and take them to school and teach them what they should go and look for in that person's cancer, we know how to do that now.

I think now the big barrier is to figure out how do we take the successes with melanoma, with leukemia, with lymphoma, with some cases of lung cancer and kidney cancer, and get this to work for everything.

It should. Every cancer is making abnormal proteins, which the immune system should be able to see. But cancers are very clever in hiding that. And if we could activate in every situation—pancreatic cancer, brain cancer, prostate cancer, breast cancer, ovarian cancer, all the places where we still don't do very well—and get the immune system to work there, then we could really declare victory.

We have got a long way to go, but, boy, it is so different than where we were a few years ago where we weren't sure this was ever really going to work. And now it clearly is. We just need to expand that effort. And the Moonshot is making that possible.

Mr. BUCSHON. I am glad you highlighted the importance of funding basic science research and how that really over decades sometimes leads to things that you don't necessarily think it might lead to, but it gets you to a place where we are today, especially as it relates to immunotherapy.

Dr. COLLINS. That is a great point. Thank you.

Mr. BUCSHON. Thank you. I yield back.

Mr. GUTHRIE. The gentleman yields back.

The gentleman from California, Ms. Eshoo, is recognized for 5 minutes for questions.

Ms. ESHOO. Thank you, Mr. Chairman.

It is wonderful to see both of you here.

And, Dr. Collins, I always like to say to my constituents that NIH stands for our National Institutes of Hope.

And I think that you have both spoken to that today with not only your opening statements, but in your answers to questions to members. So thank you for your special leadership for people in our country.

Dr. Gottlieb, in the 21st Century legislation Congresswoman Susan Brooks and myself had a bill that was included, Strengthening Public Health Emergency Response Act, and it established a priority review voucher, a PRV, to encourage the development of medical countermeasures, countermeasure drugs and vaccines at FDA.

And I know that the FDA plans to issue guidance to address this. I would like to get maybe a quick update from you on the timeline of that guidance.

Dr. GOTTLIEB. I appreciate the question, Congresswoman. I can get back to you specifically. I believe that that guidance is going to be out before the spring. I can give you a more specific timeframe on that.

Ms. ESHOO. OK. That would be wonderful.

And under the current legislation, the PRV sunsets in 2023. But if a product were being developed today, many of them need more time. So 5 years would bring us to the middle of a development cycle. Are you concerned about the uncertainty that that would yield?

Dr. GOTTLIEB. As you know, Congresswoman, the 21st Century Cures Act also provided for GAO to undertake a more comprehensive look at the PRVs more generally, and I think we are looking forward to that evaluation to have a better sense how these are impacting development and how they are providing an incentive for sponsors to try to develop therapies against some of these unmet needs that Congress is looking to target additional incentives towards.

So we are hopeful that that will help validate some of what the early experience has been, but I think we are really looking towards that report to answer some of these questions.

Ms. ESHOO. Good. Thank you very much.

Under the original legislation, the 21st Century Cures Act, H.R. 6, that the House passed, and we are celebrating its first anniversary today, the funding was mandatory. And then the final legislation authorized the increases to FDA and NIH, but didn't appropriate funding, making it subject to the annual appropriations process.

So for all that the legislation calls for, which is obviously very important, how are both of your agencies doing with the appropriations process?

Really, up front, because when the SPRO was put into this thing I just rolled my eyes, because we wouldn't have a drop of oil left in that strategic reserve if everything that claims to be funded by it were actually funded. And I understand that that is only part of it.

But how are we doing?

Dr. COLLINS. So my understanding is—and, again, this was pretty complicated financial negotiation—that the way in which this now applies is that the funds provided by 21st Century Cures do get allocated. All it requires is for the appropriators to basically—

Ms. ESHOO. I know how it works. I am just asking, is it working for you? Are you getting enough money to do what you need to do in the timeframe that you have set forward and the challenges of the legislation? I know what the process is.

Dr. COLLINS. OK. I got it. I am sorry.

Ms. ESHOO. You don't need to repeat that. I already said it.

Dr. COLLINS. We are in fact able to utilize the funds that came forward in fiscal year 2017. We look forward—

Ms. ESHOO. Of course you can use them, that is not the point. Are you getting what you need in terms of funding for the first year of a 10-year period?

Dr. COLLINS. Yes, we are.

Ms. ESHOO. How about you, Dr. Gottlieb?

Dr. GOTTLIEB. We have been allocated the funds that we expected to date.

Ms. ESHOO. Good.

Dr. COLLINS. I will tell you, I ran into Chairman Cole in the hallway coming here. He wanted all of you to know that he loves the fact that you provided funds to NIH, but he wishes that somehow——

Ms. ESHOO. Well, we don't provide funds.

Dr. COLLINS. Well, in a way. But he wishes that somehow people who gave him his allocation would pay attention to what he needs also. I had to pass that along from Chairman Cole.

Ms. ESHOO. Well, he can talk to Members. He doesn't have to give you the message.

I just want to add one more thing, and that is that I think not enough spotlight has been placed on this going to our future scientists and researchers, that this tax bill that is moving through the Congress in terms of graduate and postgraduate education is a killer. It is an absolute killer. So that should be part of the record.

Thank you, gentlemen, very much.

Mr. CARTER. [presiding.] The gentlelady yields back.

The gentlelady from Indiana, Mrs. Brooks, is recognized for 5 minutes for questions.

Mrs. BROOKS. Thank you, Mr. Chair.

And before my colleague from Colorado has to go to another hearing probably, I just wanted to thank her and former Chairman Upton for working with both sides of the aisle to get the most important piece of legislation. I have been here 5 years. I think it is the most impactful and important piece of legislation that I have been involved in. I am very proud of it.

I also was very proud to have worked with Congresswoman Eshoo on the piece of legislation that got included in this.

I want to ask you, Dr. Gottlieb, to follow up just a little bit more, since we did get included the medical countermeasures, which for the record, just to make sure, these are specific material threats identified by the intelligence community as posing a material threat sufficient to affect national security or that has been determined to seriously threaten national health security.

And there is no commercial market for this. This is why we had this limited priority review voucher. And it is seen as our private sector partners' very real incentive to continue to develop critical vaccines, whether it is things like Ebola or Anthrax or other types of threats.

Now, since we have gotten this passed, has the FDA seen an increase or a renewed interest from the private sector partners in engaging with the FDA in the medical countermeasure space?

Dr. GOTTLIEB. I would have to get back to you with the specifics, Congresswoman. I know we have had some engagement with sponsors. I would have to get back to you to let you know how far along that engagement is. We have had pre-IND and some discussions with sponsors, I am aware of that.

Mrs. BROOKS. We would welcome you getting back with us because that is what the point of it was, was trying to make sure that the private sector had the incentives in which to engage, and we need to know what is working and what is not working.

You also in your written testimony talked about the FDA's emergency use authorization, the 2017 guidance extending authorities

to be applicable to animal drugs. Can you share any updates or any hurdles the FDA has faced or potential challenges in implementing this emergency use authority?

Dr. GOTTLIEB. The EUA authority now out now applies to animal drugs, as you have said. I would have to get back to you, again, in terms of where we are talking to sponsors. I am not aware of the interactions that we have had to date. But we see this as a big opportunity to potentially give EUA to drugs targeted to animals where if you had a pandemic, for example, where the infection was transmissible to the animal and they can become a vector, you want to be able to treat the animal as well in the kind of a setting.

Mrs. BROOKS. Thank you for explaining that so well because that is so very important. We focus on people, but because animals can transmit so many diseases, I think that is critically important.

Dr. COLLINS, in my time remaining, can you talk with us a little bit more with respect to the Precision Medicine Initiative, the focus on the All of Us Research Program. And I understand when I was in another hearing you might have spoken about it already a bit. But obviously this large group of volunteers from around the country that are going to be providing genetic data, biological samples, and so forth, a new growing field.

What are some of the challenges you are seeing or what are your hopes for this All of Us Research Program? Can you talk about it a bit further?

Dr. COLLINS. My hopes are that with a million participants this is going to be the most significant study ever undertaken to identify what the factors are that allow people to stay healthy, because many of these participants will be healthy, and if illness happens, what is the best way to manage it?

So we will have such an enormous database. It will be accessible, with all the personal identifiers removed, to researchers who have qualified ideas to try the learn from it.

It will also be a platform where many clinical trials can also get started because these participants will have been preconsented for contact to see if they would be interested in taking part in a clinical trial, say, for diabetes or Alzheimer's risks. So that should greatly speed up the ability of doing all kinds of research that now is slow and expensive.

But I think most of all, to be part of this, these millions folks are going to teach us things about health in America that we just didn't know and how we can move from the one-size-fits-all approach, which is kind what we are stuck with most of medicine, into something that is much more individualized, the precision medicine idea.

It will take a while for this to build up its strength in terms of what it is going to teach us about medicine. But over the course of the coming years, I don't think very many things will happen in terms of understanding health without somebody pointing out what all of us told us because of the size and scale of that effort.

Mrs. BROOKS. You have contracted or you are entering into partnerships, if I am not mistaken, with hospitals, various community health centers, I assume—

Dr. COLLINS. Yes.

Mrs. BROOKS. —the VA, to be a part of this.

Dr. COLLINS. All of those.

Mrs. BROOKS. Will the other researchers that might not be affiliated with those institutions have access as well?

Dr. COLLINS. Absolutely. Anybody who is qualified to be able to put forward a hypothesis that is scientifically reasonable will have access. We are not trying to limit this at all. The joy that I hope will come out of this is these discoveries which will come from people who maybe didn't even know they were interested in this but had a great idea.

Mrs. BROOKS. And how will people be recruited to be participants?

Dr. COLLINS. So those who are currently covered by health provider organizations that have signed on to be our partners will be approached. But anybody in the United States will be able to join.

When we launch this next spring, you will see a lot about this. We hope all the Members of Congress will decide to join. It will simply mean getting on the Internet, reading some material, deciding about a consent, giving a blood sample, and doing a very simple physical exam.

Mrs. BROOKS. Thank you very much. Thanks for your work.

I yield back.

Mr. CARTER. The gentlelady yields back.

The gentleman from New York, Mr. Engel, is recognized for 5 minutes for questions.

Mr. ENGEL. Thank you very much.

And let me say, I have long been a committed advocate for those suffering from rare diseases in their families. I was the author of the ALS Registry Act and the two most recent Muscular Dystrophy CARE Act reauthorizations.

And the work has shown me how great the need is for new therapies and just how much hope and comfort medical breakthroughs can bring to patients and their families. And that is why I was pleased to support the passage and contribute to the 21st Century Cures Act.

So thank you to both doctors for being here today and for helping us carry this important work forward.

Let me ask both of you this question. I feel that there should be formalized, straightforward ways to gauge the safety and efficacy of medical treatments, and that is why I worked to ensure that language on biomarkers was included in the 21st Century Cures. These tools are valuable. They tell us the state of a person's health. It can help make these kinds of evaluations better.

I was happy to work with Congresswoman McMorris Rodgers to include provisions on biomarker development qualification. I know that the FDA regularly employs biomarkers during the drug approval process, but there has not been a formal procedure in place for biomarker development and use.

My understanding is that a lack of taxonomy and evidentiary standards has made it difficult to develop workable biomarkers that can be replicated during the drug approval process.

So I am wondering if each of you would talk a bit more about how NIH and FDA will work with each other, industry, academia, and other stakeholders, to develop better biomarkers and improve the way they are used for clinical trials and drug approvals.

Dr. COLLINS. I will start. Congressman, I appreciate the question because that is something of intense interest for both of our agencies.

For several years we have run something called the Biomarkers Consortium, which is a joint NIH/FDA/industry effort to try to identify opportunities where biomarkers that seem to be potentially valuable in terms of predicting response to therapy can be validated, and there has been a lot of activity in that space.

More recently, take an example of cancer, this new Partnership for Accelerating Cancer Therapies, PACT, has as its main goal identifying biomarkers for cancer immunotherapy that could be folded into the way in which we make selections about which clinical applications are going to work.

We worked with the FDA a year or so ago also to develop a biomarkers glossary so that we could all really agree about what the terminology means. You mentioned that taxonomy can sometimes be a little tangled up. So we have an agreed-upon way of using the language and the terminology.

But I will turn it over to my colleague, because obviously this is critical for figuring out how best we can come to approve therapies.

Dr. GOTTLIEB. I will just add briefly, Congressman, I think this is another place where Cures and the provisions that you worked on, you talked about, have given us important new tools to create a framework that is going to lead to more development of these kinds of biomarkers.

To give you some sense of what we have already achieved, we have entered into or received 11 letters of intent around the qualification of biomarkers through the provisions that you crafted for the development of drug development tools and have engaged with 10 external sponsors already around the development of these biomarkers.

And we have even more engagement with especially the development of clinical outcomes assessment tools also, which are another element that have become critically important to try to foster more efficient drug development.

So that might not sound like a big number. In our estimation it is a profound number given the fact that these are still early days in the development of these new frameworks and we are seeing this level of interest.

Mr. ENGEL. Thank you. Thank you both.

Dr. Gottlieb, I want to focus on biomarkers. So let me ask you this question. With respect to the section of 21st Century Cures on qualification of drug development tools like biomarkers, the proposed FDA workplan for 21st Century Cures Act Innovation Account activities says: "Once fully implemented, this section has the potential to transform drug development and review."

Could you expand on that, please? And how do you think that drug development tools like biomarkers will affect patients on the real world level? And how soon will we see these effects?

Dr. GOTTLIEB. Well, one of the challenges in the past was that when we had validated tools that were used to help make drug development itself more efficient, in many cases those tools were validated in the context of a single clinical trial, and that clinical trial was the intellectual property of a single sponsor. They didn't be-

come tools that were in the public domain that could be easily used by other sponsors who could then piggyback on these kinds of opportunities to use biomarkers as a way to facilitate more efficient development.

I think what Congress foresaw in the development of this new framework was the ability to have consortia and other entities, academic institutions, others, develop biomarkers that can become part of the public domain and become tools that many sponsors could use in an efficient fashion to help make their development programs more efficient.

So we are very helpful that this new framework, which it is an entirely new paradigm and way of thinking about the development of biomarkers as drug development tools, is going to lead to a lot of new opportunities.

Mr. ENGEL. Well, I want to thank both of you for excellent testimony and also for excellent work. Thank you so much.

Thank you, Mr. Chairman.

Mr. CARTER. The gentleman yields back. Now the chair will recognize himself for 5 minutes for questions.

Let me begin by thanking both of you for being here and both of you for the important work that you do.

Dr. Gottlieb, I will start with you. I wanted to ask you about the executive order that was signed by President Trump the beginning this year that had to do with the one-in, two-out rule of regulations that were being imposed by the agencies, a rule, by the way, that I very much support and am very happy that he put into place.

But I was just wondering, has this really impacted you in any way in trying to implement care or cures?

Dr. GOTTLIEB. Not in a negative fashion, Congressman. We have periodically over the course of the history of the agency taken opportunities to do periodic looks at our regulations to make sure that they are not outdated, that they are still having their intended purpose. And I think that the executive order provides us another good basis to do that, and that is an important exercise.

We have certainly been able to find places where there are regulations that are outdated or maybe no longer relevant that we think perhaps we could repeal in its entirety. I mentioned a couple of times we have a regulation defining standards of identity for the baking of cherry pies. We have one such regulation on the books.

But keep in mind that the executive order applies to regulations that are imposing new regulatory burdens. Many of our regulations are deregulatory. In many cases we are promulgating regulations that are actually saving money and making the process itself more efficient.

So we have been able to operate very efficiently under that framework, and we think it is a constructive framework.

Mr. CARTER. Great.

Dr. Gottlieb, you and I have spoken many times. As you know, currently I am the only pharmacist serving in Congress. And of importance to me and all of my colleagues, of course, is the opioid epidemic in our country.

One of the things that I have pushed as a pharmacist has been the fact that in my mind there is a gap, if you will, I refer to it as a gap, between what physicians can prescribe for pain, that

being Tylenol, Acetaminophen, Tramadol, if you will, and then you go to the opioids. And I refer to that as the big gap there.

Now, once you get past perhaps Lyrica and Neurontin, you really don't have any other choice but to go to the opioids. And as part of Cures and as part of CARA, you have been given the authority in the FDA of streamlining, of fast-tracking some of these non-addictive treatments.

First of all, have you gotten from the pharmaceutical manufacturers any applications for these type of drugs? And have you done anything to implement this?

Dr. GOTTLIEB. We are seeing the development of what you would refer to as nonaddictive opioids, drugs that maybe hit the same receptor but through a different pathway and might not have the same addictive qualities. I mean, it still needs to be demonstrated through rigorous science whether in fact that is going to hold true.

But we are seeing the development of these kinds of products. As you know, some of them are in early stages of development. Such products would qualify potentially for all the opportunities for expedited review, including breakthrough therapy status, and that would be something that would be confidential, however, unless the sponsor chose to disclose it.

I would also pull into the discussion the development of medical devices, because we talk about systemic therapy for the treatment of pain in many situations where the pain itself is very localized. And there is a way to, through a more sophisticated device, deliver anesthesia locally. You can potentially prevent the application of systemic therapy.

And so we are seeing those opportunities as well, and we are going to be taking steps in the near future to try to incentivize those kinds of opportunities.

Mr. CARTER. And you of course understand how imminent this problem is and how we need help. So I suspect this will be on the top of your to-do list.

Dr. GOTTLIEB. It is on the top of my to-do list.

Mr. CARTER. Dr. Collins, I suspect NIH is very much involved in this in collaboration as well. I know that your Partnership for Accelerating Cancer Therapies is something that you have been working on to address really the cancer problem, but my hope is that this is something that you will duplicate, if you will, to deal with the opioid problem as well.

Dr. COLLINS. And we are in fact deeply engaged in that, Congressman. We will in fact on December 12th and 13th hold a meeting of 33 pharmaceutical company representatives, NIH and FDA, building on studies that we have carried out over the last few months to really put in place a framework for a public-private partnership that has never been tried before, to do exactly what you are talking about, to develop these nonaddictive but highly potent pain medicines, which we desperately need.

I will just point out this morning in the New England Journal there are two publications on the development of monoclonal antibodies against something called CGRP that are showing great benefit for migraine for people who have been resistant. It is a good example of a nonaddictive kind of pain medicine working on a very different pathway than opioids.

We have a lot of basic science we can build on now to do that, but we need the full partnership of industry as well, and I think everybody is ready to do that.

Mr. CARTER. There is no question in my mind about it. As I have said, over my years of practice in pharmacy I have seen nothing short of miracles come out from the research and development from the pharmaceutical manufacturers. They need to step up now and they really need to help us with this problem. This is a national epidemic, and I am very confident that if they set their minds to it, they can do just that.

Dr. COLLINS. They are ready to do just that. It has been really quite exciting working with companies over the course of the last 6 or 7 months to see just how ready they are to roll up their sleeves and put their time and resources into this problem.

Mr. CARTER. Absolutely. And I appreciate you, both of you, and your cooperation in assisting them and fast-tracking this as much as we can.

OK. The chair now recognizes the gentleman from Missouri, Mr. Long, for 5 minutes for questions.

Mr. LONG. Is that because I am the only one left?

Mr. CARTER. Yes, sir.

Mr. LONG. Thank you, Mr. Chairman.

I want to reiterate what my friend Congresswoman Brooks next to me said earlier. And that is, when people ask me, "What is your biggest accomplishment in Congress? What are you the most proud of?" Just 21st Century Cures, period, case closed.

And that was done in a huge bipartisan fashion. As Chairman Upton mentioned earlier, 51 to nothing out of this committee, which you never see. And there were a lot of people that had a big part in that, such as Diana DeGette and Chairman Upton.

And I would be remiss without mentioning my buddy, Super Max, right here on the front row, who was a big reason that we got that through, and he attended a lot of hearings.

And thank you, Super Max.

But we do a lot of things in a partisan fashion here in Washington, unfortunately, I think, most of the time. But one thing that we did do in a bipartisan fashion was 21st Century Cures.

And also, there were a lot of folks that when they looked out at a hearing here in the 115th Congress and were looking at the Director of the National Institutes of Health, a lot of us got together from both sides of the aisle and said we would like to see you sitting there again. And so that came to fruition also.

So it is an honor to have both of you gentlemen here today. It truly is.

Dr. Gottlieb, I am going to ask you a couple of questions here. 21st Century Cures included a provision to facilitate better dissemination of healthcare economic information, and in January the FDA published draft guidelines on this issue.

Could you discuss any feedback FDA has received from stakeholders? And what do you think is working well? And are there any ways you think that communication could be improved?

Dr. GOTTLIEB. Thank you for the question, Congressman.

I think this is a very important provision of Cures. I think to the extent that we can facilitate a more seamless exchange of informa-

tion between product manufacturers and payers, we can incentivize the development of different kinds of contracting arrangements that maybe could allow products to be priced more closely to value.

I think this is an important element of trying to make sure we have a competitive market for how products get priced in the market. So I think that this is important to clarify what FDA's role is and isn't in regulating this information.

You are right, we received a lot of questions with respect to the draft guidances that were put out almost a year ago. We are going to be finalizing those guidances in the very near future. I said before the end of this year earlier, we might slip slightly into the new year in terms of when we get out those final guidances.

But our aim will be to go beyond what we did in the draft guidances to try to create a framework that provides for the free exchange of this kind of information and articulates, as Congress intended, that FDA doesn't intend to play a role in regulating the exchange of useful information in this context, even if it might have some authority to do that.

Mr. LONG. You note in your testimony that the use of real world evidence could help streamline clinical development and could help inform the safe and effective use of medical products. Could you speak to the FDA's efforts to incorporate real world evidence into regulatory decisionmaking?

Dr. GOTTLIEB. We are already seeing those efforts come to fruition, in part owing to the authorities and the nudge that we got from Congress that you wanted us to make more widespread use of this evidence, especially as the tools for collecting this evidence and drawing conclusions on the basis of it got more sophisticated.

We recently approved a supplemental indication on a heart valve based entirely on real world evidence gathered from a patient registry. And we have also granted supplemental indications to some drugs in part on the basis of real world evidence that was derived from real world data.

So this is becoming a part of the regulatory process. I think where it is going to have even more prominent application is in the post-market setting where we are opening up a framework for sponsors to be able to satisfy their post-market requirements on the basis of real world data or real world evidence collected from real world data.

Mr. LONG. OK. Thank you.

And I noted earlier that—of course things pop into my mind that don't pop into other people's mind—but when you were talking about gene therapy, just as you said that, Gene Green walked in.

So I think it is a different gene therapy, unless you want to tell us something, Gene.

I yield back.

Mr. CARTER. The gentleman yields.

The chair recognizes the gentlelady from Indiana, Mrs. Brooks.

Mrs. BROOKS. Thank you for allowing me to speak out of order, Mr. Chairman.

My good friend and colleague from Missouri, Mr. Long, besides acknowledging that it was awesome to have Max and his mom here, and I want to thank him, but I also want to acknowledge that a Hoosier family has also been here, Laura McLinn and her son

Jordan, who is back in the office. He suffers from Duchenne Muscular Dystrophy, and they have also been active in Indiana in advocating for Cures. And I just wanted the folks who are testifying and who are devoting their lives to know that this matters to so many families. And I just wanted to acknowledge them for being as here as well.

Thank you. I yield back.

Mr. CARTER. The gentlelady yields back.

Seeing there are no further members wishing to ask questions, I would like to thank all of our witnesses again for being here today.

I would like to submit a statement from the Healthcare Leadership Council for the record.

[The information appears at the conclusion of the hearing.]

Mr. CARTER. And pursuant to committee rules, I remind members that they have 10 business days to submit additional questions for the record. And I ask that witnesses submit their response within 10 business days upon receipt of the questions.

Without objection, this subcommittee is adjourned.

[Whereupon, at 12:31 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]



November 28, 2017

The Honorable Michael C. Burgess, M.D.
Chairman
U.S. House Energy and Commerce
Subcommittee on Health
2125 Rayburn House Office Building
Washington, D.C. 20515

The Honorable Gene Green
Ranking Member
U.S. House Energy and Commerce
Subcommittee on Health
2322A Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Burgess and Ranking Member Green:

The Healthcare Leadership Council appreciates the opportunity to submit this letter regarding the Energy and Commerce Subcommittee on Health hearing on "Implementing the 21st Century Cures Act: An Update from FDA and NIH."

The Healthcare Leadership Council (HLC) is a coalition of chief executives from all disciplines within American healthcare. It is the exclusive forum for the nation's healthcare leaders to jointly develop policies, plans, and programs to achieve their vision of a 21st century health system that makes affordable, high-quality care accessible for all Americans. Members of HLC – hospitals, academic health centers, health plans, pharmaceutical companies, medical device manufacturers, laboratories, biotech firms, health product distributors, pharmacies, post-acute care providers, and information technology companies – advocate for measures to increase the quality and efficiency of healthcare through a patient-centered approach.

HLC appreciates the committee's bipartisan efforts toward the passage of the "21st Century Cures Act." This law contains important provisions that will advance the rate of cures and treatments for millions of Americans.

Research:

HLC has been a strong proponent of important initiatives that were included in the 21st Century Cures Act. Specifically, HLC supports the Innovation Fund, which advances important initiatives at the National Institutes of Health (NIH), including the Precision Medicine Initiative, the Cancer Moonshot Initiative, the BRAIN Initiative, and the Regenerative Medicines Initiative. We encourage the administration to continue

working with the private sector on these and other crucial research efforts by reducing barriers to broader data sharing among private sector and government entities.

Specifically, we encourage the administration to allow private sector organizations greater access to research identifiable files for regular, systematic use that proactively evaluates the safety and effectiveness of medical products and services. Currently, these files are only made available to researchers on a per-study basis. We also encourage the administration to streamline the process by which the Centers for Medicare and Medicaid Services (CMS) approves researchers, as the current process is extremely long and administratively burdensome. Finally, we urge the Department of Health and Human Services (HHS) to harmonize CMS data use agreement protections (as required by the Privacy Act of 1974 and Privacy Act regulations in 45 CFR Part 5b) with the data use agreement provisions in the HIPAA privacy rule. Data use agreements should follow a standardized format across all federal government agencies.

Medical Devices and Drugs:

HLC supports many of the medical device and drug provisions included in the 21st Century Cures Act. We look forward to the Food and Drug Administration's (FDA's) implementation of these provisions, which aim to reduce the regulatory burden associated with medical device and pharmaceutical product regulation. We particularly appreciate an expedited review process for breakthrough devices as well as simplifying the process for exempting certain devices from the premarket notification requirement. We also look forward to working with the FDA as it establishes its program to evaluate the potential use of "real world evidence" in support of applications for new indications for FDA-approved drugs.

Health information technology:

HLC has a long history of promoting health information systems' interoperability across organizations and applauds Congress for including important provisions in the 21st Century Cures Act that advance nationwide interoperability. HLC members look forward to working with HHS as the agency develops regulations related to practices by health information technology vendors and healthcare providers who intentionally block or otherwise inhibit health information exchange. In 2014, the CEOs of HLC declared their opposition to technology products and practices that block or otherwise inhibit health information exchange. HLC supports efforts by policymakers to address products and practices that intentionally block the sharing of information, or that create structural, technical, or financial impediments or disincentives to the sharing of information.

Mental health and substance use disorders:

Finally, HLC appreciates the shift in thinking in the 21st Century Cures Act that promotes advances in treating mental health and substance use disorders. Enhanced cooperation among agencies and providing funding for the development of innovative evidence-based models of treatments to address mental health and substance use disorders is an important step forward provided by the Act.

To build on these important advances, HLC encourages the committee to promote greater data sharing to coordinate the care of patients dealing with mental health or substance use disorders. Specifically, we urge the committee to pass H.R. 3545, the Overdose Prevention and Patient Safety (OPPS) Act, which would enable providers to better treat those suffering from substance use and alcohol disorders by aligning their substance use information with their medical information under the HIPAA privacy rule. This holistic approach to effectively treating patients suffering from addictive disorders is long overdue.

We applaud the committee's leadership to ensure swift and appropriate implementation of the 21st Century Cures Act and look forward to working with the committee and the administration on this effort. If you have any questions, please do not hesitate to contact Tina Grande, Senior Vice President for Policy at HLC, at (202) 449-3433 or tgrande@hlc.org.

Sincerely,

A handwritten signature in cursive script, appearing to read "Mary R. Greal".

Mary R. Greal
President

GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115
Majority (202) 225-2927
Minority (202) 225-3641

December 18, 2017

The Honorable Scott Gottlieb
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

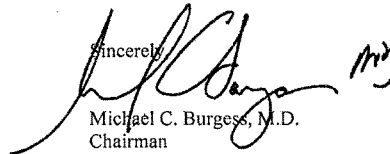
Dear Dr. Gottlieb:

Thank you for appearing before the Subcommittee on Health on November 30, 2017, to testify at the hearing entitled "Implementing the 21st Century Cures Act: An Update from FDA and NIH."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on January 8, 2017. Your responses should be mailed to Zack Dareshori, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to zack.dareshori@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Michael C. Burgess, M.D.
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

Committee on Energy and Commerce
Implementing the 21st Century Cures Act: An Update from FDA and NIH
November 30, 2018

FDA Questions for the Record

We have restated your questions below in bold, followed by our responses.

The Honorable Michael Burgess

1. **A goal of 21st Century Cures was to help the transition between research generated by NIH and regulated by FDA. Are there areas where this could be improved? One challenge is that NIH funds new clinical trials that may become difficult to complete because a new drug is approved mid-way through the trial for the condition being researched. Could a "memorandum of understanding" allow for pre-approval data to be shared from FDA to NIH earlier in the process to improve coordination of research and regulation?**

As public health agencies within the Department of Health and Human Services, FDA and the National Institutes of Health (NIH) may generally share with each other most information in the possession of either agency. Sharing of information between FDA and NIH is subject to prohibitions against disclosure of non-public information and must include appropriate safeguards to prevent unauthorized disclosure, which are incorporated into existing memorandums of understanding between the two agencies. That being said, FDA evaluates whether information can be disclosed on a case-by-case basis. Although FDA may be able to share certain confidential information with NIH, that information may not be able to be shared with an NIH grantee, contractor, or cooperative research and development partner. Given that NIH studies may involve commercial entities (e.g., funding or IND sponsor), it is critical for FDA to consider whether disclosure of non-public information to NIH could cause commercial harm to the applicants who submitted the information to FDA.

FDA approval of a new treatment does not generally impact the status of ongoing trials in a disease area unless the treatment provides an improved safety and/or efficacy profile relative to the investigational treatment. In those cases, it could be unethical to deprive a clinical trial participant of the opportunity to obtain the newly approved treatment. After approval of a new treatment, FDA may reach out to trial sponsors if any modifications are needed for ongoing trials to treat the same disease for which the new treatment is indicated. Often, whether the newly FDA-approved treatment is safer or more effective than an investigational treatment in an NIH-funded trial will not have been established at the time of approval; under those circumstances, it would generally be appropriate to continue conducting the trial.

2. **The Least Burdensome Provisions of the FDA Modernization Act of 1997 have been in statute for some time. This concept-that FDA should regulate medical devices in the least burdensome manner, while not sacrificing patient safety-is critical to ensuring that we have reasonable regulation, and avoid the issue of regulation for regulation's sake.**

Page 2 – The Honorable Michael C. Burgess, M.D.

21st Century Cures included a provision to require FDA to conduct an audit on training and use of least burdensome requirements during review of medical devices. Can you tell us what FDA has been doing to implement this section of the law?

FDA has taken several steps to implement the Least Burdensome provisions of the 21st Century Cures Act (Cures Act). As required under the Cures Act, FDA has provided training on the least burdensome requirements to all employees (including supervisors) involved in the review of device premarket submissions, and has conducted an audit of the training.

FDA has also taken steps to improve our application of the least burdensome principles more broadly. FDA believes that least burdensome principles should be widely applied across the total product lifecycle for medical devices to remove or reduce unnecessary burdens so that patients can have earlier and continued access to high-quality, safe, and effective devices and we can more effectively use our limited resources on actions that will improve the health and quality of life of patients.

In recent draft guidance, FDA defines “least burdensome” to be the minimum amount of information necessary to adequately address a regulatory question or issue through the most efficient manner at the right time. The least burdensome principles are based on sound science, the letter and intent of the law, the use of alternative approaches, and the efficient use of resources to effectively address regulatory issues. FDA has significantly broadened the scope of least burdensome principles by expanding their application to all aspects of the total product life cycle for medical devices rather than just select premarket activities. Beyond the requirements of the Cures Act, FDA’s Center for Devices and Radiological Health (CDRH) has required that all of its employees, not just employees involved in medical device review, receive training on the least burdensome provisions and principles. CDRH required that its entire staff be trained because it believes the least burdensome concept is foundational to its work with respect to the regulation of medical devices.

3. **Supplemental indications, or additional uses for a drug, can be added to the product label when the sponsor provides the necessary data to the FDA to support these new uses. In many cases, the FDA treats each application associated with a drug the same, whether it is the first indication or the eighth indication. Given that aspects of a drug, such as its toxicity profile, becomes better understood over time, a provision was included in 21st Century Cures to improve the efficiency of reviewing potential new uses of a drug by allowing the FDA to review summaries of data rather than internally re-analyzing the complete raw datasets themselves. I understand this is completely up to the FDA to determine when this approach is appropriate, and the review team would have access to the full data at any point. Has this provision been used? How frequently? Do you foresee instances where this can improve efficiency?**

Authority added under section 3031 of the 21st Century Cures Act provides that FDA may rely on qualified data summaries to support approval of a supplemental application for a qualified indication of a drug if certain conditions are met. FDA intends for the initial focus of FDA’s

implementation of this authority to be on supplemental applications for oncology drugs. We are currently in the process of evaluating criteria for identifying supplemental applications that may qualify for this type of review and the appropriate processes for facilitating and evaluating such review.

4. Patient-focused drug development was an aspect of 21st Century Cures that garnered a significant amount of attention. The law requires the FDA to provide guidance on the use of relevant patient experience and patient input data, including with respect to the structured risk-benefit assessment framework, to inform regulatory decision making. The 21st Century Cures Act provides a timeframe of 5 years for the FDA to issue such guidance. Could you share your thoughts on the impact patient experience perspective data will have on the drug development front, particularly with respect to the risk-benefit framework?

FDA considers information from patients about what matters most to them in living with their disease to be of the utmost importance. As such, FDA conducted 24 patient-focused drug development (PFDD) meetings over the past five years. These meetings confirmed the Agency's perspective that patients are experts in what it is like to live with their disease and that drug development and patients would benefit from greater integration of patients' voices in drug development. Patients are uniquely positioned to inform FDA's assessment of the *severity of a disease condition* and the *degree of unmet medical need* based on their report of experience with currently available therapies. These are the first two of five key considerations that FDA weighs within its framework for assessing the benefit and risk of a medicine.

Patients may also be able to more formally and systematically report on their experience of benefits and risks while participating in clinical studies of investigational drugs. These reports can inform other key considerations of the benefit-risk framework: the evidence of *benefit* and *risks*, based on data collected in clinical trials, and potential approaches to *risk management* to ensure that expected benefits outweigh risks for patients taking the medicine.

Patient experience data has the potential to inform a number of aspects of drug development. These data can inform a sponsor's development of a target product profile for an investigational drug. They can inform the development of data collection instruments that will capture the patient's experience more systematically, and they can inform the development of targeted endpoints that can be used to assess therapeutic benefit. In addition, patient experience data may be collected to inform the design and planning of clinical trial operations to facilitate patient enrollment and sustained involvement in studies by making them more convenient and less burdensome for patients who participate. All of these opportunities contribute to the quality of a drug development program and the evidence collected to assess the benefit versus risk of the new medicine.

The range of potential uses of patient experience data call for a corresponding range of data collection and analysis methods that will be sufficiently rigorous to ensure the quality to achieve the desired goal of patient impact on drug development and regulatory decision making. The guidance that FDA will be developing to implement section 3002 of the 21st Century Cures Act,

Page 4 – The Honorable Michael C. Burgess, M.D.

will provide drug sponsors and the patient advocacy community with a set of tools to collect and utilize patient experience data that are fit for this purpose.

FDA's actions in patient-focused drug development include:

- Holding 24 PFDD meetings, each focusing on a different disease area.
- Outlining the steps FDA will take over the next five years to provide guidance on collecting patient experience data and using such data and related information in drug development. (See "Plan for Issuance of Patient-Focused Drug Development Guidance Under 21st Century Cures Act."¹)
- Developing "The Voice of the Patient: A Series of Reports from FDA's Patient-Focused Drug Development Initiative"² and "Voice of the Patient" blog.³
- Establishing a new Patient Engagement Collaborative⁴ to incorporate perspectives from patients, caregivers, and advocates into the FDA's regulatory decision-making processes.

How patients feel and function in their daily lives is a crucial component of determining the risk-benefit balance in treating diseases. FDA considers patient-identified disease impacts and measures of benefit and burden as early as possible in the drug development and review processes. Improved methodologies for accurately measuring these factors will advance the ability of FDA to systematically incorporate patient feedback into the risk-benefit framework.

The Honorable Cathy McMorris Rodgers

When asked about the scope of pharmacy practice this summer, you noted that a prescription provides a "line of demarcation" defining the practice of pharmacy and that "the statute clearly defines in my mind the line of demarcation for the legitimate practice of pharmacy." This statement is consistent with the policies expressed in the guidance document entitled "Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act," which states that unless a limited exception applies "to qualify for exemptions under section 503A, the drug product must be compounded after the licensed pharmacist or licensed physician receives a valid prescription order for an individual patient." Unfortunately, this view differs with FDA policies over the past two years. The agency has redefined the distribution of a sterile compounded preparation to include patient specific dispensing in the draft MOU and repackaging guidance (among other guidances). This, in my opinion, appears to run counter to the DQSA's statutory language, the Food Drug and Cosmetic Act, as well FDA's traditional interpretation of the

¹ <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM563618.pdf>

² <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm>.

³ <https://blogs.fda.gov/fdavoices/index.php/2014/05/fdas-voice-of-the-patient-listening-to-those-most-affected-by-their-disease-and-treatments/>

⁴ <https://blogs.fda.gov/fdavoices/index.php/2017/07/patient-reps-bringing-the-voice-of-patients-to-fda/>

definitions of "distribute" and "dispense" and will reduce access to compounded sterile preparation prescriptions.

1. Please share with the committee your thoughts on the definitions of "dispense" and "distribute", and how you plan to align the MOU and other guidance with Congress' and your understanding of pharmacy practice.

The proposed policy articulated in the draft standard memorandum of understanding (MOU) concerning the term "distribution" is consistent with the policy articulated in the final guidance, "Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act."⁵ In that guidance, the Agency explained that compounding under section 503A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) can occur either after the receipt of a valid prescription order for an identified individual patient (section 503A(a)(1)), or in limited quantities before the receipt of a valid prescription order for an identified individual patient (section 503A(a)(2)). The guidance explains that section 503A does not provide for the *distribution* of a compounded drug before, or without, receiving a valid prescription for an identified individual patient.

FDA proposed that the term "distribution" for the purposes of the draft standard MOU means that a compounded human drug product has left the facility in which the drug was compounded, which includes dispensing a drug directly to a patient. In comments regarding the draft standard MOU, some members of the pharmacist community asserted that the definition of distribution should exclude dispensing. According to these comments, this is in part because some in the pharmacist community understand distribution to refer to the shipment of compounded drug products *without* patient-specific prescriptions, and dispensing to refer to the shipment of compounded drug products *with* patient-specific prescriptions. However, to qualify for the exemptions under section 503A of the FD&C Act, a compounder must obtain a prescription for an identified individual patient (section 503A(a)). The definition of distribution in the draft standard MOU is consistent with the prescription requirement under section 503A, described in FDA's final guidance document on this subject.

We note that FDA received more than 3,000 comments on the draft standard MOU, including many comments regarding the term "distribution," and comments describing overall access concerns. FDA is taking these comments into consideration as we work diligently to issue a revised draft standard MOU in the coming months.

With respect to FDA's repackaging guidance, FDA issued the final guidance in January 2017,⁶ after taking into consideration all of the public comments that it received. FDA believes that the policies articulated in this and other final guidances, including the use of the term "distribution," are in the best interest of the public health.

The Honorable Marsha Blackburn

⁵ <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf>.

⁶ <https://www.fda.gov/downloads/Drugs/Guidances/UCM434174.pdf>.

Page 6 – The Honorable Michael C. Burgess, M.D.

1. **I was glad to speak with you back in July when you called to tell me about your implementation of my SOFTWARE Act with the Pre-Cert for Software Pilot Program and the announcement of the companies selected to participate. Could you please provide this committee with an update on the pilot program, including feedback from the nine participating companies? What lessons has the agency learned so far about how best to regulate innovative, low-risk devices and software?**

FDA has completed its initial visits to all nine pilot participants. The feedback was positive and all of the participating companies are engaged. FDA looks forward to building a program that best serves public health by fostering the development of innovative, safe, and effective digital health products. We have learned the ways in which excellent companies in the digital health space are the same and the ways in which they are different from one another. We intend to propose a streamlined, risk-based approach that capitalizes on the commonalities and allows for differences that support positive innovation. We held a public meeting in January where FDA presented its finding to date; sought other perspectives; and incorporated input from a broader set of stakeholders – including patients, providers, payers, and others in industry. .

The Honorable Ben Ray Lujan

Thank you for your response on November 7, 2017, to my letter asking the Food and Drug Administration (FDA) to take concrete steps to enable and communicate the availability of safe and effective, non-opioid drug products. As you know, millions of Americans require clinical treatment for pain relief. I was glad to see that we are in agreement about the importance of combating the opioid epidemic, as you wrote in your November 7 letter. 1

In light of FDA's belief that all healthcare providers involved in the management of pain should be educated about the safe use of opioids, I would appreciate information related to the following questions:

1. **You wrote, “For the first time, FDA announced its intention to require immediate-release (IR) opioid analgesic products to be subject to the same REMS requirements.” You also note that you expect the modified REMS to include revisions related to prescriber education.**
 - a. **What is the agency’s timeline to finalize a modified REMS? What considerations is the agency taking into account when considering changes to the education requirements related to the REMS?**

FDA expects to finalize the modified REMS approximately 1 year following issuance of the REMS Notification letters (issued September 28, 2017). FDA considered stakeholder feedback on the education component of the Opioid Analgesics REMS received:

- At the joint meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) held on May 3-4, 2016

Page 7 – The Honorable Michael C. Burgess, M.D.

- At the May 9-10, 2017, public workshop - Training Health Care Providers on Pain Management and Safe Use of Opioid Analgesics – Exploring the Path Forward
- To Docket No. FDA-2017-D-2497 - Draft Revisions to the Food and Drug Administration Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioids

Based on the stakeholder feedback, the content of the “Blueprint” for education will be expanded to include principles related to acute and chronic pain management; non-pharmacologic treatments for pain; and pharmacologic treatments for pain (both non-opioid analgesic and opioid analgesic). The revised Blueprint will also cover information about the safe use of opioids, and basic information about addiction medicine and opioid use disorders. The education will also be expanded to other healthcare professionals who are involved in the management of patients with pain, including nurses and pharmacists, which is in addition to prescribers of opioid analgesics.

2. **You wrote, “The new training will be aimed at making sure providers are prescribing opioids only for properly indicated patients, and only under appropriate clinical circumstances [...as] part of a broader effort to take new steps to make sure providers are properly informed about suitable prescribing and the risks and benefits associated with opioid drugs.**

a. What additional activities does FDA’s broader effort include? Who within FDA is responsible for this broader effort to inform providers about suitable prescribing?

FDA’s Opioid Policy Steering Committee is considering novel ways to reduce the number of new cases of opioid addiction. FDA recently held a public hearing entitled, “Opioid Policy Steering Committee: Prescribing Intervention – Exploring a Strategy for Implementation.” The purpose of the public hearing was to receive stakeholder input on how FDA might, under its Risk Evaluation and Mitigation Strategy (REMS) authority, improve the safe use of opioid analgesics by curbing overprescribing to decrease the occurrence of new addictions and limit misuse and abuse of opioid analgesics.

Recent studies suggest that prescriptions for opioid analgesics are frequently dispensed for a number of tablets that exceed those needed for adequate pain control, particularly for acute pain. The Steering Committee is exploring, by means of FDA’s REMS authorities, the option of facilitating appropriate prescribing by requiring sponsors to implement a prescriber intervention at the point when the prescriber determines an opioid analgesic prescription is necessary for a patient. For example, a REMS could impact prescribing by requiring that sponsors ensure that prescribers provide specific documentation for a prescription above a specified amount. Such a documentation requirement would be designed to ensure that prescribers consider whether the amount prescribed is appropriate for the patient and, if above the specified amount, document that necessity.

The Steering Committee is also considering whether to require sponsors to create a system that would leverage a nationwide database to be more effective in helping healthcare providers identify potential misuse and abuse (e.g., doctor shopping) and facilitate safe use of opioid analgesics (e.g., real-time identification of potential harmful drug-drug combinations). Such an

Page 8 – The Honorable Michael C. Burgess, M.D.

approach could be integrated into the healthcare provider's workflow to minimize burden on the health care system.

In addition, the Steering Committee is seeking input on whether, consistent with the Agency's statutory authority, FDA should require sponsors to take additional measures to ensure that healthcare providers, their patients, and patient caregivers and family members are educated on safe storage and disposal and the risks of misuse, abuse, and addiction associated with opioid analgesics (for example, a public health campaign targeted at these groups).

Finally, FDA is working with medical professional societies to potentially create expert guidelines about what appropriate prescribing and dispensing should be for different medical needs. These efforts align with those of the Centers for Disease Control and Prevention (CDC). If guidelines were in place and had sufficient scientific support, and FDA reviewed the scientific support for these guidelines and determined that it was sufficient to support updates to product labeling, then we could potentially use our current authority to adjust product labeling, thereby promoting more appropriate prescribing.

3. You wrote, "There have been a small number of non-opioid drug shortages over the past few years, but there continue to be multiple alternative options available to patients."

a. What are these multiple alternative options to non-opioid drugs that are available to patients? How many alternative options to non-opioid drugs are available to patients?

Alternatives to opioids (e.g., non-opioid drugs) to treat various types of pain, along the spectrum of severity, include the following approved non-opioid products:

- NSAIDs (non-steroidal anti-inflammatory drugs) of which there are many (ibuprofen, diclofenac, ketorolac, etc.)
- duloxetine (Cymbalta) is included in the class of drugs called selective serotonin/norepinephrine reuptake inhibitors (SNRIs), and is approved for diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain
- milnacipran (Savella, also an SNRI) for fibromyalgia
- gabapentin (Neurontin, Gralise), pregabalin (Lyrica), and carbamazepine (Tegretol) (originally approved as anticonvulsants, each are indicated for treatment of specific types of neuralgia and other neuropathic pain)
- topical lidocaine (local anesthetic), and capsaicin
- ziconotide by intrathecal infusion for chronic pain.

4. You wrote, "There are few existing classes of analgesics." In Division Director of the Division of Anesthesia, Analgesia, and Addiction Products Dr. Sharon Hertz's March 1, 2016 presentation to the FDA Science Board, she listed existing analgesics as opioids,

nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, antidepressants, local anesthetics, and “other (capsaicin and ziconotide).”⁷

- a. Are these six classes a comprehensive list of existing analgesic drug classes? If not, what additional or alternative classes are there?

This list is comprehensive at this time.

5. You wrote, “Drug developers may encounter both clinical and nonclinical challenges specific to their drug development program.”

- a. What are some examples of clinical and nonclinical challenges that drug developers have faced?

Examples of clinical challenges include difficulty enrolling subjects, study designs, finding qualified study sites to conduct studies. An example of a nonclinical challenge is identifying appropriate pain models for study. Nonclinical models tend to be poorly predictive of clinical success in this area.

- b. Is there a trend of where in the development or regulatory processes the challenges are faced?
For example, are the challenges primarily in the review or in the post-market phase?

Most challenges in the development or regulatory processes occur premarket.

- c. What are some potential incentives to increase the number of non-opioid drugs in the pipeline?

Where applicable, the expedited review programs FDA has in place to aid development may apply to some non-opioid analgesics under development and can assist industry in more efficient drug development. More information about FDA’s expedited review programs can be found on our website.⁸

- d. Is the main challenge increasing the number of drugs entering the pipeline, or increasing the number of drugs coming out of the pipeline?

One of the biggest challenges for new analgesics is identifying new targets that have high specificity for pain pathways so that the product works, with as little affinity for non-pain targets as possible to reduce the risk of side effects. This limits the number of drugs entering

⁷ Hertz, Sharon, Division of Anesthesia, Analgesia and Addiction Products, OND, CDER, FDA, “Challenge of developing new pain medicines – developing novel analgesics and abuse-deterrent formulations,” March 1, 2016, <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM489207.pdf>.

⁸ <https://www.fda.gov/ForPatients/Approvals/Fast/default.htm>

the pipeline. The Agency works closely with sponsors from the earliest stages of development to provide advice based on our vast experience with analgesic drug development, to permit the most efficient development program possible, and to advance the approval and marketing of safe and effective pain drugs.

e. Do you consider FDA barriers to be clinical or nonclinical?

As discussed above, examples of clinical challenges include enrolling subjects, study designs, finding qualified study sites to conduct studies and examples of nonclinical challenges include identifying appropriate pain models for study as nonclinical models tend to be poorly predictive of clinical success in this area. These challenges for drug developers can result in both clinical and nonclinical data limitations as those developers make submissions to FDA.

6. You wrote, “The Agency is open to working with sponsors who are interested in developing new potential treatments.”

Have any sponsors already asked FDA to work together to develop new potential treatments? If so, what did FDA respond?

FDA is committed to the principles of open government and transparency. At the same time, FDA must comply with its obligations to keep certain information in its possession confidential. We do not publicly release correspondence regarding potential new treatments before the approval of an application. Therefore, FDA is unable to publicly disclose specific data used in making recommendations for a particular treatment.

From a broader perspective, FDA has past and ongoing work in the development of novel treatments for pain and opioid overdose, supported through our participation in the ACTION public private partnership (PPP)⁹ and other PPP and consortia initiatives in a wide variety of areas relevant to pain treatment, opioids, substance use treatment, drug safety, and accelerated drug development.

- The Consortium for Addiction Research on Efficacy and Safety (CARES) is working to create consensus on the design and analysis of addiction clinical trials, which would be a valuable step towards reducing barriers to drug development.
- The Agency and the National Institute on Drug Abuse (NIDA) are discussing mechanisms to collect data to support the use of new endpoints for trials of drugs intended to treat opioid substance use disorder.
- FDA and NIDA are also working to encourage the development of non-opioid pain medications, and we have been involved in discussions hosted by the National Institutes

⁹ The Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks Initiative (ACTION) aims to streamline the discovery and development process for new analgesic drug products for the benefit of the public health. This multi-year, multi-phased initiative will address major gaps in scientific information which can slow down analgesic clinical trials and analgesic drug development (see <http://www.action.org/>).

of Health (NIH) and the Foundation for NIH (FNIH) in a series of meetings to facilitate development of non-addictive pain treatment. These efforts will be pursued in partnership with FDA and the Centers for Medicare and Medicaid Services (CMS) to ensure that products can quickly move from discovery and development to approval and implementation in clinical practice.

- The Coalition for Accelerating Standards and Therapies (CFAST) is an initiative to accelerate clinical research and medical product development by facilitating the creation and maintenance of data standards, tools and methods for conducting research in therapeutic areas important to public health.

7. You wrote, “Moving forward, we strongly encourage manufacturers and drug developers to contact the Division of Anesthesia, Analgesia, and Addiction Products in the Center for Drug Evaluation and Research so that we can provide targeted advice specific to their drug development program.”

Have any manufacturers contacted DAAAP in CDER to request targeted advice specific to their drug development programs? Has FDA provided targeted advice specific to drug development programs?

As stated above, FDA must comply with its obligations to keep certain information in its possession confidential. We do not publicly release information pertaining to anything under review until it has been approved. We encourage sponsors to contact us early and often in their drug development program and work closely with them to assure that thresholds of safety and effectiveness are addressed in submissions provided to FDA.

8. You wrote, “For more information, please see our draft guidance entitled *Analgesic Indications: Developing Drug and Biological Products*, which, when finalized, will provide the Agency’s recommendations on such development.”

The draft guidance was released in February 2014, “for comment purposes only.” It had a 60-day comment period. Since February 2014, approximately 190,000 Americans have died due to opioid overdoses.¹⁰ Is FDA currently in the process of finalizing the guidance? If available, when does FDA anticipate publishing the finalized guidance?

Subsequent to the release of the draft guidance, our advisory committees have provided advice about analgesic development that we have been working to translate into useful guidance for industry. We are also incorporating input from the National Academies of Sciences, Engineering, and Medicine (NASEM) 2017 report, “Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use”, particularly, how to frame the risk/benefit analysis to demonstrate the many public health factors that are taken into consideration when making regulatory decisions about new analgesic products. Even

¹⁰ “1,396 days between February 2014 and November 2017; according to CDC estimates, 50,000 Americans died from an opioid overdose in 2016, which is 137 people per day, Time Magazine, “Here’s what it would cost to fix the opioid crisis, according to 5 experts,” <http://time.com/money/5032445/cost-fix-opioid-crisis/>”.

Page 12 – The Honorable Michael C. Burgess, M.D.

though the draft guidance has not yet been finalized, FDA works with individual sponsors on development issues.

9. You wrote, “We have been involved in discussions with the National Institutes of Health in a series of meetings to facilitate development of non-addictive pain treatment.”

What is the structure of this series of meetings? Who is the designated point person at FDA and who is the designated point person at NIH for these meetings? Can I communicate directly with those point people for the meetings? What are the goals of these meetings? Are these meetings open to the public? How many meetings are in the series? How many have already been held? How many are scheduled to occur? When do these meetings occur? Where do these meetings occur?

NIH is the lead HHS agency providing support for cutting-edge research on pain and opioid misuse, addiction, and overdose. NIH is exploring ways to work with private sector partners to promote safe, effective, non-addictive strategies to manage pain as part of a broader public-private partnership aiming to cut the time needed to develop new therapeutics to help end the opioid crisis.¹¹ NIH is also exploring ways to facilitate development of additional treatments for opioid use disorder. To advance the efforts, since June 2017, NIH has held three seminal meetings with the pharmaceutical industry, researchers, FDA and other experts in pain and addiction. NIH has been in discussions with over 30 companies and FDA in a joint effort to advance this initiative. Meetings were held on December 11 and 12, 2017 to bring stakeholders together to identify areas of scientific opportunity that could be pursued in collaboration with industry partners.

10. You wrote, “Novel non-opioid medications with the potential to provide effective pain relief, and that satisfy the applicable legal criteria, may be appropriate candidates for such programs,” referring to “programs, such as Fast Track and Breakthrough Therapy Designation, which are intended to facilitate the development and expedite the review of products that, for example, are intended to treat a serious condition for which there is an unmet medical need.”

How many non-opioid products are currently under review for management/treatment of pain? Of the current products under review, how many/what percentage have applied for and been awarded one of these designations? Are there other tools at your disposal to move these applications through in a timely fashion? If not, what can Congress do to help? In addition to new product approvals, please describe how manufacturers can seek new indications, expanded labels and/or different concentration approvals for non-opioid products already available to patients.

As noted above, FDA must comply with its obligations to keep certain information in its possession confidential. We do not publicly release correspondence regarding potential new treatments before the approval of an application. Therefore, FDA is unable to publicly disclose specific data regarding any products that may be under review.

¹¹ <https://www.nih.gov/research-training/medical-research-initiatives/opioid-crisis/public-private-partnership>.

Currently, both opioid and non-opioid FDA-approved drugs are available for the management of pain. There are also medical devices indicated to treat specific types of pain, such as intrathecal pumps that have been cleared to administer morphine and ziconitide for chronic pain.

The Commissioner has made addressing the opioid addiction epidemic among one of his highest priorities. FDA understands the value in, and supports the development of, new treatment options for pain, and continues to work with the medical device and drug industries to explore new options for patients in pain, especially options that have improved safety profiles and are less likely to result in addiction or abuse. The tools in our expedited programs have been helpful in facilitating the development and expediting the review of products. For example, FDA approved Evzio, the first auto-injector formulation of naloxone, and Narcan Nasal Spray, a nasal spray formulation of naloxone hydrochloride, in less than four months under expedited review. These are the first approved opioid overdose treatments specifically designed so that they can be administered by family members or caregivers in the community. FDA also approved Narcan Nasal Spray as a 2 mg formulation for the emergency treatment of known or suspected opioid overdose through an expedited pathway.

Manufacturers can seek new indications, expanded labels and/or different concentration approvals for non-opioid products already available to patients by following the requirements set forth in 21 CFR 314.70 and by reviewing our guidances, such as *Guidance for Industry: Changes to an Approved NDA or ANDA*.¹²

¹² <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm077097.pdf>.

GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115
Majority (202) 225-2927
Minority (202) 225-3641

December 18, 2017

The Honorable Francis Collins
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

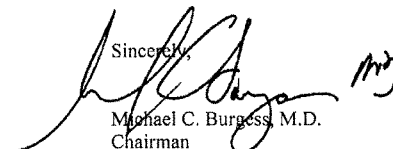
Dear Dr. Collins:

Thank you for appearing before the Subcommittee on Health on November 30, 2017, to testify at the hearing entitled "Implementing the 21st Century Cures Act: An Update from FDA and NIH."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on January 8, 2017. Your responses should be mailed to Zack Dareshori, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to zack.dareshori@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Michael C. Burgess, M.D.
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

Committee on Energy and Commerce
Implementing the 21st Century Cures Act: An Update from FDA and NIH
November 30, 2017

NIH Questions for the Record

The Honorable Michael Burgess

1. A goal of 21st Century Cures was to help the transition between research generated by NIH and regulated by FDA. Are there areas where this could be improved? One challenge is that NIH funds new clinical trials that may become difficult to complete because a new drug is approved mid-way through the trial for the condition being researched. Could a "memorandum of understanding" allow for pre-approval data to be shared from FDA to NIH earlier in the process to improve coordination of research and regulation?

NIH Response:

NIH is committed to speeding the translation of research into improved diagnostics, preventive interventions, and new treatments for patients. The agency works closely with the FDA on improving strategies for doing so through better coordination between the research funded by NIH and the regulatory process overseen by FDA. For example, the NIH-FDA Leadership Council recently established an open access textbook: the Biomarkers, EndpointS and other Tools (BEST) Resource. Biomarkers, or biological markers, are indicators of a condition or disease in the body. These important research tools can be used to measure how well the body is responding to a treatment, for example, and are key indicators used in the regulatory process to evaluate new drugs. The first phase of BEST comprises a glossary that NIH and FDA plan to use when communicating about biomarkers to help ensure a consistent use of terms and a common understanding of issues. In addition, NIH's National Center for Advancing Translational Sciences' (NCATS) Therapeutics for Rare and Neglected Diseases (TRND) program benefits from early interaction and coordination of research with the FDA. A working group of TRND program staff and FDA staff from the Center for Drug Evaluation and Research (CDER) meet on a semi-monthly basis to discuss projects for the TRND program with the goal of an Investigational New Drug Application for each project. TRND staff take FDA/CDER feedback into consideration when developing future project plans, aiming to create a more efficient and successful drug development process.

NIH is exploring mechanisms to enable greater discussion among Federal agencies of upcoming and recent potential regulatory actions and clinical development plans of FDA-regulated products. Such discussions with FDA could include sensitive and proprietary information, although issues around protecting proprietary data, what information can be shared, and when in the process it is best to coordinate would need careful consideration. This type of coordination may prevent investments by government agencies in concepts that have already been studied and could provide key information in developing pre-clinical models for therapy development. Joining FDA data with NIH efforts could produce new opportunities for research coordination and regulation.

2. As you know, the NIH has made some changes to the definition and requirements regarding clinical trials in order to improve thoroughness and transparency. Can you walk through those changes and the impact on both the patient and the research community? What is the NIH doing to address any concerns and confusion from those in the grantee community who will be impacted by these changes?

NIH Response:

As the largest funder of clinical trials in the U.S., NIH is dedicated to strong leadership of the clinical trial enterprise. NIH strives to ensure that trials are: relevant to NIH's mission; not duplicative of previous efforts; and, are designed, conducted and reported in a manner that will optimize the likelihood of successfully advancing knowledge and expanding options to improve patients' health. To this end, NIH launched a multi-faceted effort to strengthen how researchers and their institutions develop ideas, design and conduct clinical trials, how NIH chooses which projects to support and oversee progress, and how trial results are shared. The ultimate goal of this effort is to elevate the entire biomedical research enterprise to a new level of transparency and accountability.

These stewardship reforms, which involved extensive public input, include implementation of the NIH definition of a clinical trial among other initiatives such as:

- Dedicated funding opportunity announcements for clinical trials to improve NIH's ability to identify proposed clinical trials, ensure that key pieces of trial-specific information are submitted with each application, and uniformly apply trial-specific review criteria.
- Good Clinical Practice training for NIH-funded investigators and staff who are involved in the conduct, oversight, or management of clinical trials to help assure safety, integrity, and quality.
- Enhanced registration and results information reporting on ClinicalTrials.gov, with the expectation that all NIH-funded clinical trials are registered at, and that summary results information is submitted to, ClinicalTrials.gov for public posting. Increasing the transparency of clinical trial results, among other benefits, will strengthen the design of future clinical trials.
- Use of Single IRBs for multi-site studies to minimize duplicative reviews, allow research to proceed efficiently and expeditiously, and maintain optimal protections for human research participants.
- Development of a clinical trial protocol template and electronic protocol-writing tool to help investigators think through the scientific basis of their assumptions, minimize uncertainty in the interpretation of outcomes, and prevent loss of data.

Impact on Patient Community

NIH's efforts to enhance stewardship of clinical trials aim to produce more efficient and higher quality trials, so that scientific knowledge – and ultimately safe and effective treatments – will be available more quickly. The single IRB policy and protocol template address current delays and inefficiencies in trials by streamlining current processes for protocol review and supporting compliance with FDA regulations for Investigational New Drug applications. Dedicated funding opportunities announcements, which include rigorous review criteria for trials, help NIH ensure

only the highest-quality clinical trials are funded, while Good Clinical Practice training holds researchers and NIH staff to a high standard for quality and safety. Finally, increased transparency, achieved through ClinicalTrials.gov registration and results information reporting, will not only help patients and providers identify relevant clinical trials, but also increase public access to the results of clinical trials.

Also, as part of these efforts, NIH is making ClinicalTrials.gov more user-friendly so that patients, family members, and physicians can more easily find clinical trials that may be right for them. In September 2016, NIH formed a partnership with 18F, a digital services consultancy within the General Services Administration, to explore ways to increase the site's usability. Following a series of consultations with stakeholders, updates to ClinicalTrials.gov in 2017 include resizing pages to fit different devices; new fields to refine a search, including by U.S. state; an improved search results page that provides new ways to refine results; and the ability to download search results in various formats. Collectively, these and other changes will enable patients to more quickly navigate the website to find clinical trials relevant to their condition.

Impact on Research Community

Enhancing stewardship of clinical trials and promoting transparency affects investigators and staff responsible for designing, managing, conducting, and overseeing clinical trial research, institutions that are responsible for clinical trials, research participants involved in clinical trials, and NIH staff who are responsible for stewardship of clinical trials. These enhancements will improve the application and award processes, augment NIH's ability to assess clinical trial applications, improve transparency and accountability, and increase sharing of clinical trial results. NIH is committed to continuing to work with the research community to implement these initiatives and engage in discussion with and outreach to stakeholders as needed, or as concerns arise.

Responsibilities of researchers and their institutions include 1) correctly identifying whether their research meets the NIH definition of a clinical trial; 2) applying to the correct Funding Opportunity Announcement and creating applications responsive to the clinical trial review criteria; 3) completing Good Clinical Practice (GCP) Training; 4) complying with the sIRB policy; and 5) registering and reporting results information in ClinicalTrials.gov. NIH is helping investigators and their institutions with these changes through efforts including the following:

- NIH has developed a website with comprehensive information, including case studies and FAQs to help clarify for our research community whether their research study meets the NIH definition of a clinical trial. These resources prompted follow-up questions and suggestions from the research community, which helped NIH refine these documents. NIH considers these informational materials to be living documents, which we will continue to build on and clarify with input from the scientific community.
- NIH has developed tools to help institutions complete their applications, including a video tour of the new Human Subjects and Clinical Trial information form, an annotated application form set, and a summary of changes between the previous and new forms packages.
- NIH is developing a new electronic system to provide more streamlined management and oversight of human subjects and clinical trial information. The system, expected to be

available by summer 2018, will facilitate monitoring and reporting and enhance strategic planning and portfolio analysis.

- In response to input from the scientific community, NIH extended the effective date for the sIRB policy from May 2017 to January 25, 2018 to give investigators and their institutions more time to prepare for the changes. In addition, NIH has [developed FAQs on implementation of the sIRB policy](#), which include links to example standardized agreements that will allow institutions to rely on a single IRB of record for multisite studies.
- Several NIH Institutes have created free online GCP training. [Links to these trainings](#) are available on the NIH website. [FAQs](#) are available to provide guidance to the research community.
- NIH has developed a [decision tree](#) outlining steps to compliance with ClinicalTrials.gov results information reporting and registration requirements.
- Continued outreach and discussion with all affected research communities to support the goals of these initiatives.

The complementary activities described here intend to help fulfill the NIH mission of improving health through scientific discovery, while preserving the public trust in research through efficient and transparent clinical trials. Working together with the public and the scientific community, these efforts allow NIH to enhance scientific stewardship, dissemination of information, transparency, and to excel as a federal science agency.

- 3. We've heard a lot about how the 21st Century Cures Act has helped eliminate red tape for extramural researchers, so they can spend less time on paperwork and more time on science. Can you tell us about how these provisions have helped your researchers over the last year?**

NIH Response:

For decades, NIH has focused on reducing administrative burden in various ways including but not limited to, leading efforts within the Federal Demonstration Partnership and supporting efforts coordinated by the Office of Science and Technology Policy. NIH Director Dr. Francis Collins is co-chair of the National Science and Technology Council's Committee on Science, and NIH is a co-chair of the Research Business Models Working Group, an interagency working group under the CoS, formed to facilitate a coordinated effort across Federal agencies to improve coordination and collaboration among research agencies to streamline requirements for the extramural community.

As an example of NIH's efforts to reduce administrative burden and in response to the FY15 omnibus report language requiring NIH to initiate an Administrative Burden Workgroup, NIH engaged and was actively involved in a collaborative effort to address the issue of administrative burden with the ad hoc committee of the National Academies of Science convened to study Federal regulations and reporting requirements with specific attention to those directed at research universities. The resulting report, "Optimizing the Nation's Investment in Academic Research: A New Regulatory Framework for the 21st Century" was issued in two parts: Part I focused on those regulatory issues identified as of most pressing concern to the research

community while Part II contains the analysis of topics that adversely affect the nation's ability to optimize its investment in academic research.

The report recommended harmonizing existing policies and processes across Federal agencies (e.g. uniform format for grant proposals and research progress reporting) as well as reducing the regulatory burden associated with policies for human subjects' research, animal care and use, monitoring of sub-recipients, reporting of financial expenditures, and disclosure of financial conflicts of interest. In addition, the Committee recommended that Congress establish the Research Policy Board (RPB), which would serve as a public-private forum for discussions relating to regulations of federally-funded research. Subsequently, the 21st Century Cures Act requires the Office of Management and Budget to establish the RBP to provide Federal Government officials with information on the effects of regulations related to Federal research requirements.

The 21st Century Cures Act signed into law on December 13, 2016, legislates requirements designed to reduce administrative burden by modifying and harmonizing regulations and policies having similar purposes across research funding agencies to ensure that the administrative burden is minimized to the greatest extent possible while maintaining responsible oversight of federally funded research. NIH has implemented several of these provisions including eliminating Paperwork Reduction Act requirements for scientific studies, and automating the issuance of certificates of confidentiality as a "term and condition of award" for awards involving human subjects so NIH-funded researchers no longer need to request one. Further efforts to streamline applications for clinical trials, effective for due dates on or after January 25, 2018, include a structured data form for human subjects research fields that eliminates duplicate information entries. In addition, NIH and FDA partnered together to develop a clinical trial protocol template¹ with instructional and example text for NIH-funded investigators to use when writing protocols for phase 2 and 3 clinical trials. NIH developed a simplified application appendix² to rectify inequities in peer review that arise from submission of inappropriate or excessive appendix materials.

NIH continues to work with DHHS to decrease burden involved in financial conflict of interest reports, reducing audit burden by raising the threshold, waiving the requirement for subrecipient monitoring when the subrecipient is in good standing, and simplifying and harmonizing animal care regulations.

NIH is partnering with ORCID³ to enable scientists to include additional data fields useful to maintain and update biosketches and CVs across multiple platforms. ORCID is a not-for-profit organization that assigns unique persistent identifiers to researchers that supports automated linkages between researchers and their professional activities with the goal of helping people find information and to simplify reporting and analysis. NIH's eRA Commons, an online interface where signing officials, principal investigators, trainees and post-docs at institutions/organizations can access and share administrative information relating to research

¹ [NIH and FDA Release Protocol Template for Phase 2 and 3 IND/IDE Clinical Trials](#)

² [Updated Appendix Policy Eliminates Clinical Trial-Related Materials for NIH/AHRQ/NIOSH Applications Submitted to Due Dates on or After January 25, 2018](#)

³ [Teaming with ORCID to Reduce Burden and Improve Transparency](#)

grants, is establishing a real-time link with ORCID, which allows users to associate ORCID with their eRA account. Further, NIH and other funders are collaborating on the ORCID Reducing Burden and Improving Impact Tracking (ORBIT) project. This effort will expand the ORCID data model beyond publications to data elements typically found on a CV, such as grants, courses taught, presentations, and other research products. To this end, in 2017, NIH developed guidance on how NIH applicants have the option, for applications submitted for due dates of May 25, 2017 and beyond, to cite interim research products such as preprints in applications.

NIH continues to consider ways to address the recommendations to reduce the administrative burden associated with Federal research funding outlined in the NAS report and 21st Century Cures Act. For some of these recommendations, NIH can take action by implementing changes to grant policies.

Because all of the provisions of the 21st Century Cures Act have not been fully implemented, it is too early to determine the effect on research. However, NIH is diligently working with university faculty and research administration staff to ensure that measures implemented by NIH to reduce administrative burden are effective.

4. **The 21st Century Cures Act included language addressing medical rehabilitation research at the NIH. The language changed the requirements for this research, including revise the purpose of the National Center for Medical Rehabilitation Research, or NCMRR, and transfer responsibility for developing a comprehensive research plan to NCMRR from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. What steps has the Office of the Director, in coordination with NCMRR, taken to implement the rehabilitation research provisions in Cures?**

NIH Response:

The National Center for Medical Rehabilitation Research (NCMRR) in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development was established to promote rehabilitation research within the National Institutes of Health, coordinate NIH's research efforts across Institutes and Centers, and foster collaboration with other federal agencies. Together, they provide funding for research projects, career development, small business efforts, and research infrastructure. NCMRR oversees implementation of the updated provisions of Section 2040 of the 21st Century Cures Act; implementation is well underway.

A scientific workshop on the state of rehabilitation research was held in the spring of 2016. This widely attended workshop informed the development of the 2016 NIH Research Plan on Rehabilitation, which was published in late 2016. The Plan, which will be next updated in 2021, sets forth NIH's research priorities in five major areas: Rehabilitation Across the Lifespan, Community and Family, Technology Use and Development, Research Design and Methodology, Translational Science, and Building Research Capacity and Infrastructure. The NIH Rehabilitation Research Coordinating Committee, led by NCMRR, coordinates the NIH's efforts in carrying out the Plan's priorities. Most recently, for example, NCMRR has worked with other NIH Institutes and Centers, and other federal agencies, to sponsor research workshops on Clinical Trials in Rehabilitation (2016) and Optimizing the Investment in Medical Devices for Rehabilitation (2017). In addition, NICHD recently awarded new grants to support research

infrastructure in rehabilitation, including biomechanics and modeling of movement, and regenerative medicine. Working with other NIH Institutes, multiple funding opportunities on aspects of rehabilitation research also have been published, seeking grant applications on sleep disorders in the context of medical rehabilitation, and tailoring cardiac rehabilitation to enhance participation of older adults, among others.

The first analysis of the rehabilitation research portfolio at NIH is complete and was presented as part of NCMRR's annual report at the December 2017 meeting of the National Advisory Board for Medical Rehabilitation Research. Additional data tracking the first two years of changes in the portfolio following the publication of the research plan will be provided to the Board at its May 2018 meeting. The reporting of rehabilitation research is consistent with the definition in Section 2040 and, as required, the Director of NIH's Division of Program Coordination, Planning, and Strategic Initiatives is now an active member of the Advisory Board to facilitate coordination with the NIH Office of the Director.

5. **Part of the intent of 21st Century Cures was to support better collaboration in research and further trans-NIH initiatives. One opportunity for such an initiative would be in better understanding how individuals with three copies of chromosome 21, which causes Down syndrome, are protected from certain cancers and heart attacks, but are more likely to succumb to Alzheimer's disease, childhood leukemia, and certain autoimmune disorders. It is my understanding that Trisomy 21 is unique in that it is the only genetic condition with these co-morbid condition connections. Do you see any opportunities for enhanced coordination among NIH Institutes to better unlock the secrets of Down syndrome, and in turn identify ways to prevent and treat Alzheimer's? How can precision medicine advance this goal?**

NIH Response:

One benefit of communication and collaborations across NIH Institutes and Centers, and with the Down syndrome community, is increased coordination of research efforts. Led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the public-private Down Syndrome Consortium, which includes 11 NIH Institutes and Centers (ICs), 13 national and international organizations whose missions focus on Down syndrome, and individuals with Down syndrome and family members, provided valuable input to the 2014 revision of the NIH research plan on Down syndrome. *DS Directions: The NIH Down Syndrome Research Plan* has had an impact on the field of Down syndrome research; in submitting grant applications, many researchers have cited one of its objectives, particularly including the call for research on many of the comorbidities commonly experienced by people with Down syndrome (congenital heart disease, leukemia, and intestinal issues, and other developmental disorders). While life expectancy for people with Down syndrome who are living in the United States has increased dramatically over the last 50 years, these coexisting conditions still require more research and, in turn, a wider variety of expertise as represented across NIH.

Members of the Trans-NIH Working Group meet regularly about the wide-range of investigator-initiated research projects and other NIH-supported efforts to improve the health of people with Down syndrome, including those with co-existing conditions. Studies show that virtually all middle-aged adults with Down syndrome exhibit the neuropathological hallmarks of Alzheimer's

disease: amyloid senile plaques and tau-containing neurofibrillary tangles. The Alzheimer's Biomarker Consortium – Down Syndrome (ABC-DS), funded collaboratively by the National Institute on Aging (NIA) and NICHD, provides an exciting opportunity to improve our understanding of Alzheimer's disease among people with Down syndrome, 50 percent or more of whom develop brain changes associated with Alzheimer's by age 40. This initiative seeks to identify biomarkers and track the progression of Alzheimer's in people with Down syndrome, using brain imaging, as well as fluid and tissue biomarkers, to help us understand progression of the disease. In addition, NIH's Alzheimer's research agenda continues to be informed by the recommendations of the April 2013 workshop "Advancing Treatments for Alzheimer's Disease in Individuals with Down Syndrome," which was co-sponsored by NICHD and NIA, as well as the National Institute of Neurological Disorders and Stroke (NINDS), the Down Syndrome Research and Treatment Foundation and Research Down Syndrome (now merged and known as the LuMind Research Down Syndrome Foundation). To that end, NIA is supporting a Phase I clinical trial of an anti-amyloid immunotherapy for cognitive impairment in adults aged 35-55 with Down syndrome. The NIA also funds a project investigating the natural history of amyloid deposition in adults over the age of 30 with Down syndrome. This longitudinal study investigates the progression of amyloid deposition using brain imaging, while cognitive function of study participants, at the time of imaging, is also assessed to determine if there is a predictable trajectory toward clinical AD.

In addition, NIH assists the research community by providing research resources that might otherwise prove cost prohibitive for them to support individually. To advance research on Down syndrome, NICHD supports a contract for the leading repository of mouse models for Down syndrome. The Cytogenic & Down Syndrome Models Resource at Jackson Laboratory maintains and distributes mouse models for Down syndrome, as well as the study of chromosomal aneuploidy, and has recently funded a new research project to develop new mouse models for Down syndrome. The NICHD Brain Bank for Developmental Disorders at the University of Maryland, which was first funded in 1991, is now a tissue collection site (including Down syndrome). The site is part of the NIH NeuroBioBank, a partnership involving NICHD, NINDS, and NIMH, to enhance nervous system tissue collection across sites and disorders, including control samples, with a centralized IT platform and shared protocols. Efforts to promote collection of brains from adults with Down syndrome through the NIA-funded Alzheimer's Disease Centers also are being explored.

Together with NIMH and NINDS, NICHD encourages studies that develop, validate, and/or calibrate informative outcome measures for use in clinical trials for individuals with intellectual and developmental disabilities, including Down syndrome. And *DS-Connect®*, a Web-based DS patient registry that was established in 2013 and now includes about 3,700 participants, provides researchers with a tool to recruit for their research studies. The registry benefits families, too; ultimately, the registry will link to biorepositories of tissue samples and other resources, making it easier for participants to take part in clinical studies for new medications and other treatments for Down syndrome and its coexisting conditions.

Current efforts include ongoing discussions with member organizations of the Down Syndrome Consortium to help determine which objectives identified in *DS Directions: The NIH Down Syndrome Research Plan* should be prioritized, as well as efforts related to brain and

biospecimen banking. NIH IC leadership and leaders of several of the Down syndrome organizations also met in December 2017 to explore public-private partnerships to promote research interests related to Down syndrome.

The Honorable Cathy McMorris Rodgers

The 21st Century Cures Act improved upon the National Pediatric Research Network Act, which was initially crafted in 2013 with the intent to address the shortfall in pediatric biomedical research using the well-proven network model to foster greater collaboration, coordination, and sharing of resources. As an author of the underlying statute, I can tell you that our vision was that each consortium would be investigator-initiated, consist of multiple institutions in a "hub and spoke" arrangement and be competitively selected through a rigorous review process. My understanding is that the NIH maintains it has implemented the NPRNA by establishing the IDeA States Pediatric Clinical Trials Network. I support your current efforts, but am concerned about the geographical limitations on the network as well as precluding funding for all phases of scientific research other than clinical trials.

1. Do you have plans to further implement the full scope of the NPRNA, and if not, why?

NIH Response:

Pediatric research has been and continues to be an NIH priority. The NIH's strong basic research portfolio provides the foundation for pediatric research in a variety of scientific areas. In Fiscal Year (FY) 2017, the NIH funded approximately \$4.1 billion in research grants and projects directed specifically at pediatric research, an increase of \$220 million over FY 2016 spending. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) funds the largest portion of pediatric research among the 27 NIH Institutes, Centers, and Offices (ICOs), taking a leadership role in many pediatric research efforts that involve trans-NIH collaborations. However, all of the ICOs support various aspects of pediatric research, such that the NICHD alone accounts for only 18 percent of the total NIH support for pediatric research. This reflects the breadth of the research portfolio at the NIH dedicated to improving the health of children everywhere.

The NIH intends to meet the goals of the National Pediatric Research Network Act through four networks: the Environmental influences on Child Health Outcomes (ECHO) program IDeA States Pediatric Clinical Trials Network, the Pediatric Trials Network, the Neonatal Research Network, and the Rare Diseases Clinical Research Network.

The IDeA States Pediatric Clinical Trials Network (ISPCTN) provides medically underserved and rural populations with access to state-of-the-art clinical trials, apply findings from relevant pediatric cohort studies to children in IDeA state locations, and build pediatric research capacity at a national level. Funding for this new network also supports professional development of faculty-level researchers and their support teams in the conduct of clinical trials research. The awards are a component of the ECHO Program, which is investigating how exposure to a broad range of environmental factors in early development, from conception through early childhood,

influences the health of children and adolescents. It is important to note that the ISPCTN funds research centers in States where there was little to no pediatric research capacity prior to its creation.

ISPCTN consists of multiple institutions arranged in a “hub and spoke” model, with each of its 17 clinical sites in a separate IDeA state and its central Data Coordinating and Operations Center located at the University of Arkansas for Medical Sciences. ISPCTN uses this network model to foster collaboration, coordination, and sharing of resources not only within the Network but also to partner with other NIH networks focused on pediatric biomedical research to increase representation of children from beyond the IDeA states.

The Pediatric Trials Network (PTN) is comprised of over 100 clinical research sites across the U.S with over 7,000 children enrolled. The PTN provides evidence for the formulation, dosing, efficacy, and safety of medications and medical devices in infants and children. The PTN conducts pediatric clinical drug trials in a variety of therapeutic areas, including but not limited to cardiovascular diseases, cancer, infectious diseases, gastroenterology, respiratory diseases, neonatology, and medical devices. Current studies include research on the pharmacokinetic and pharmacodynamics properties of antipsychotic drugs in children and adolescents, a study on the effectiveness of sildenafil to decrease the risk of pulmonary arterial hypertension in preterm infants, and research on the pharmacokinetics of methadone to treat opioid withdrawal in children.

The NIH also supports a national network focused on neonatal research. The Neonatal Research Network (NRN) is a collaborative network of neonatal intensive care units across the United States, comprising 18 clinical centers and a data coordinating center. Focused on newborns, particularly extremely low-birth-weight infants, the NRN conducts clinical trials and clinical studies in such areas as sepsis and other infections, bronchopulmonary dysplasia and other lung conditions, and necrotizing enterocolitis, a condition in which the intestines lack oxygen or blood flow.

Finally, the NIH prioritizes research into rare diseases that affect children. The Rare Diseases Clinical Research Network (RDCRN) program, led by the National Center for Advancing Translational Sciences (NCATS) in collaboration with other NIH Institutes, is a model designed to advance medical research on rare diseases. The RDCRN currently includes 100 institutions and clinical sites in 33 States examining over 6,000 children each year. Several of the Rare Diseases Clinical Research Consortia (RDCRC) focus on or include rare diseases that affect children, including brittle bone diseases, mitochondrial diseases, immune deficiencies, Rett syndrome and Rett-related disorders, sterol and isoprenoid conditions, urea cycle disorders, genetic disorders of mucociliary clearance, developmental synaptopathies, and lysosomal storage diseases, among others.

Collectively, these networks support research capacity across the U.S. to address unmet pediatric research needs. NIH fully expects these networks to continue to expand and will continue to seek out partnerships with all stakeholders and other pediatric research consortia.

The Honorable Marsha Blackburn

2. Children sometimes fail to benefit from NIH's research because there is no existing mechanism to collect and report the ages of patients enrolled in trials, meaning we have no idea how many children participate in NIH studies. That is why I worked with Rep. Capps to include our bill, the Children Count Act, in the Cures Act to require NIH to collect this critical information. Can you please update us on how NIH plans to implement this provision and when NIH will require the information to be collected for all studies?

NIH Response:

For nearly 20 years, it has been the policy of NIH that children must be included in all NIH-supported research involving human subjects, unless there are scientific or ethical reasons not to include them. The NIH is committed to the inclusion of all relevant age groups, including children and older adults, in the clinical research studies and clinical trials it supports. Age-appropriate inclusion leads to better science and ultimately informs how interventions affect us all.

NIH has taken several steps to implement provisions in the 21st Century Cures Act requiring NIH to publish data on relevant age categories, including pediatric subgroups. These steps include:

- In April 2017, NIH announced its new FORMS-E grant application forms, required for applications submitted on or after January 25, 2018. This forms package requires investigators proposing human subjects research specify the minimum and maximum age of participants in the proposed study.
- In April 2017, NIH issued a Request for Information (RFI): Invitation to Comment on Inclusion in Clinical Research Across the Lifespan ([NOT-OD-17-059](#)) to solicit input from the scientific community and general public regarding appropriate inclusion of pediatric and older populations in research studies involving human subjects. In the RFI, NIH requested stakeholder input on age-related data, statistics, and reporting.
- On June 1-2, 2017 NIH held a workshop on Inclusion Across the Lifespan, which brought together experts in clinical research to discuss barriers and opportunities for participation of children and older adults in clinical research studies. Among the topics discussed was the need for better data on clinical research participation for children and older adults.
- At the December 2017 Advisory Committee to the Director meeting, NIH presented a proposed Inclusion Across the Lifespan policy, including a plan for collection of de-identified individual-level data on participant sex/gender, race, ethnicity, and age at enrollment.
- In December 2017, NIH revised the NIH Policy and Guidelines on the Inclusion of Children. The policy, now titled the [NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects](#), applies to individuals of all ages and requires NIH-supported clinical research studies submit de-identified individual-level data on participant sex/gender, race, ethnicity, and age at enrollment in progress reports. This policy applies to applications received on or after January 25, 2019.

NIH looks forward to the availability of additional data on the age of participants in clinical research studies. Information on the proposed age range of participants and individual-level data on age at enrollment of clinical research participants will help NIH consider and monitor the appropriateness of participant age distribution in the context of the scientific question proposed. Individual-level data on age at enrollment and other demographic variables will allow NIH maximum flexibility and detail for analyses of participant age in the NIH portfolio.

The Honorable John Sarbanes

The 21st Century Cures Act seeks to accelerate the development of new antibiotics as part of our national effort to address the increasing threat of antibiotic resistant organisms. This threat, combined with the dwindling pipeline of novel antibiotic research, requires policies that prevent inappropriate use of antibiotics.

One potential way to do that is to increase the use of penicillin allergy testing. While about 10 percent of the population reports a history of penicillin allergy, studies show that approximately 90 percent or more of these patients are actually not allergic to penicillin and are able to take these antibiotics safely. If these individuals are tested to verify they are truly allergic, they may be able to prevent the unnecessary use of broader spectrum antibiotics.

- 1. Has the NIH initiated research in this area with the goal of changing the behavior of patients and providers?**

NIH Response:

NIH has encouraged the development of research proposals on drug allergy through funding initiatives (see response to Question 2). NIH is not funding research to determine the role that confirming an individual's historical penicillin allergy may play in the prevention of inappropriate antibiotic use.

NIH continues to prioritize research to address the increasing threat of antimicrobial resistance and is an important partner in implementing the *National Action Plan for Combating Antibiotic-resistant Bacteria*. Current NIH efforts to address antimicrobial resistance and to prevent the inappropriate use of antibiotics include the investigation of the mechanisms of drug resistance and pathogenesis via foundational basic research and cutting-edge genomic sequencing technologies; detection and tracking of pathogens with simple and accurate diagnostics; development of next-generation vaccines to prevent bacterial infections; and identification of novel antibacterial drugs and treatment regimens. The NIH also is collaborating with other HHS partners on the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the global public-private partnership dedicated to the preclinical development of new antibiotics.

- 2. What initiatives has the NIH undertaken to implement the research agenda developed by a workshop on drug allergy held in 2013?**

NIH Response:

In addition to the 2013 workshop on drug allergy, which brought together U.S and international experts in the field of drug allergy, NIH held a second workshop on drug allergy in 2015. Based on the research agendas developed during these workshops, the NIH developed a drug allergy-related initiative. This effort includes two companion NIH-wide initiatives titled “Serious Adverse Drug Reaction Research” (PAR-16-274 and PAR-16-275) to stimulate new research on drug reactions, including research on drug allergy. In addition to these NIH-wide efforts, research on drug allergy also has been a focus of the NIAID initiative “Asthma and Allergic Diseases Cooperative Research Centers” (ADCRCs; RFA-AI-16-065). The ADCRC program promotes multidisciplinary basic and clinical research on the immunological basis, pathobiology, diagnosis, treatment, and prevention of asthma and allergic diseases.

